Heinz Mehlhorn

Human Parasites

Diagnosis, Treatment, Prevention

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Cover illustration: Scanning electron micrograph of a couple of the species *Schistosoma mansoni*. See also Fig. 4.1 a in this book. Photo Heinz Mehlhorn

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This edition is dedicated to my wife Birgit on the occasion of our 42th wedding anniversary.

February 2016

Preface

Parasites threaten still today the health of humans and their animals, although considerable progress had been achieved within the last century. However, phenomena such as **globalization** with the daily transportations of millions of containers and humans from one end of the world to the other make it easy for agents of disease and their vectors to suddenly occur at places which were thought to be safe. Thus, it is not astonishing that worldwide so-called **emerging diseases** occur at a formerly unbelievable speed. The ongoing **climate change** additionally offers better conditions for many agents of disease and their vectors to enter and to settle in formerly untouched regions.

Therefore, it is needed to observe intensively the development and progress of such aggressive organisms. **Parasites** belonging to the groups of protozoans, worms or arthropods may harm humans and their animals directly by entering them or indirectly as blood suckers, which may transmit other agents of diseases such as "viruses, bacteria or even parasites.

Parasite-derived diseases cause still today a considerable number of deaths, endangering millions of humans around the world, since still today the measurements to control parasites are poor in many cases. The number of treatment failures even increases constantly due to the fact that resistances of the parasites against older medicaments are rising.

Parasitology is now an interdisciplinary science, since parasites are animals which attack humans and animals. Thus, parasitic problems have to be considered by physicians, veterinarians, biologists, pharmacists, chemists, epidemiologists, etc., in order to develop successful control measurements.

The German Rudolf Leuckart (1822–1898) (Fig. 1) was the first to propose that parasitology should handle all perspectives of parasites as an own interdisciplinary field of science and not as an addendum to human or veterinary medicine.

This textbook considers the problems of humans with parasites. In order to make it easy to find quickly the relevant information, each chapter on a parasite is subdivided into 12 sections:

1. Name
2. Geographic distribution/epidemiology
3. Biology/morphology

Rud. Leuckart
W. Dickore fec.

Fig. 1 Medal showing Rudolf Leuckart (1822–1898), the “founder” of parasitology as a separate branch connecting the knowledge of physicians, veterinarians and biologists. The German Society of Parasitology honours internationally known scientists for their contributions in the fight against parasites by awarding the Rudolf Leuckart medal

4. Symptoms of disease
5. Diagnosis
6. Pathway of infection
7. Prophylaxis
8. Incubation period
9. Prepatency
10. Patency
11. Therapy
12. Further reading

More and detailed information is contained in the recently published 4th edition of Mehlhorn H (ed.) (2016) Encyclopedia of Parasitology, Springer, Berlin, New York. This book and an online version is a product of cooperation with more than 50 colleagues worldwide.

Düsseldorf
April 2016

Heinz Mehlhorn

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This English version is based on the 7th edition of a textbook in German language. This volume condenses the contents of the common books and publications with my colleagues D. Düwel, D. Eichenlaub, A.O. Heydorn, S. Klimpel, T. Löscher, W. Peters, G. Piekarski, W. Raether, E. Schein, E. Scholtyseck and many other parasitologists of my and foreign groups. I am very grateful for their intense cooperation during the last 40 years.

My thanks go also to Dr. Volker Walldorf, who contributed a broad spectrum of drawings. My wife Birgit Mehlhorn helped to collect literature and to translate this volume into English. Mrs. Inge Schaefers and Mrs. Susanne Walter brought the text in the present form. In addition, Mrs. Walter and Dipl. Ing. Isabelle Mehlhorn organized the final presentation of the figures of this book.

Mrs. Andrea Schlitzberger and Mr. Lars Körner at Springer Publishers (Heidelberg) cared for the final version of this book, which hopefully makes it easy for the reader to find quickly the wished information.

Düsseldorf
March 2016

Heinz Mehlhorn

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About the Author

Prof. Dr. Heinz Mehlhorn has investigated parasites, their transmission pathways and significant control measures for over 40 years. He has published more than 20 books and 250 original publications and received 25 patents on antiparasitic drugs, some of which he uses at his university spin-off company Alpha-Biocare (founded in 2000). As a university instructor, he had the pleasure to introduce many students to the topics in parasitology. Many of them are now professors or in leading industrial positions. In television and radio broadcasts, he regularly informs the public about relevant parasitological problems.

The Phenomenon Parasitism

1

The term **parasite** has its origin in the Greek word *parasitos*, which describes a person that tests food of mighty, noble persons in order to avoid poisoning. Since they obtained their food without paying or working for, the term got soon a negative meaning characterizing tricky, unsocial persons. From there the term was later also transferred to animals, which live fully or at least in part time on costs of their human or animal hosts.

All animals and also humans have the same problem to obtain their daily food. Apart from fully plant eaters, all other species have to strengthen their ability to catch and ingest other specimens. Thus the fittest will kill smaller and weaker individuals in order to succeed in the by Darwin (1809–1882) described **struggle for life**. However, also the individuals of weaker (smaller) species developed skills to survive either by ingesting the remnants of the meals of powerful species (i.e. **commensalism** = Latin = eating together) or by living at the surface (skin, hair) of larger animals as so-called ectoparasites (Greek = *ectos* = outside). Other parasites started invasion from the outside when entering the mouth or anus respectively started entering (totally or just by mouthparts) the skin of animals, which thus become **hosts** = prey animals.

Ectoparasites may stay **stationary** always or **temporary** for a while on their host. For example, head lice (*Pediculus humanus capitis*) are stationary parasites, since only pregnant female lice change the host, whereas female mosquitoes suck blood only at intervals on various warm-blooded hosts and leave them immediately after the successful blood meal. However, there are also many intermediate sucking activities. For example, ixodid ticks such as *Ixodes ricinus* stay up to 10–12 days on their hosts, before dropping down in order to proceed moult on the ground hidden in grass, while *Argas* ticks stay only a few minutes on their hosts during their blood meal.

Endoparasitism has its origin in activities, which are still today seen in the behaviour of scabies mites (*Sarcoptes scabies*), which enter and stay in the host's epidermis, in the case of flagellates which enter and live inside the mouth or anal regions or in *Schistosoma* species, where their free-living cercariae enter the body

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of vertebrates in order to live as adult worms finally in the blood vessels of their hosts. The intracellular way of life of stages of protozoans (e.g. *Eimeria* species, *Toxoplasma gondii*) is apparently a peculiar type of the general endoparasitism being based on the relative small size of the invading organism. But even larger organisms such as the larvae of *Trichinella spiralis* are able to live for long intracellularly.

Parasites may (depending on the species) invade one host species or several ones. Those with only one host type are described as **monoxenous**, while others with several hosts are termed **heteroxenous**. The latter parasites may be classified according to the amount of different hosts as **di-**, **poly**- or even **heteroxenous**. If a host change is absolutely needed, it is called **obligatory**; if several hosts may be selected just by occasion, the host-parasite relation is called **facultative**.

Hosts are furthermore categorized according to the fact, whether they harbour the sexual stages of the parasite (=**final host, definitive host**) or whether they contain asexually reproducing stages (=**intermediate hosts**). For example, the cat is the final host for *Toxoplasma gondii*, whereas humans and mice are intermediate hosts. However, in the case of the tapeworms *Echinococcus granulosus*, humans are only intermediate hosts (bearing the cyst with asexually reproduced protoscolices), and dogs/foxes are the final hosts bearing the adult tapeworms.

The terms **main host** and **accidental host** are less accurate since this determination is often only based on the present status of knowledge and must perhaps be changed if epidemiologic studies add other insights. For example, the main hosts for *Trichinella spiralis* are pigs and rats, while humans are mainly accidental hosts. Parasites such as *Entamoeba histolytica*, which have no (or a not yet proven) sexual reproduction, cannot become classified into the above-cited host system.

Several species of ectoparasites are described acting as **vectors**, which are able to transmit agents of diseases, which in most cases even may reproduce themselves inside these insects, ticks or leeches. Inside these vectors even the sexual development of agents of disease may occur (e.g. *Plasmodium* species – agents of malaria which proceed to gamogony in *Anopheles* mosquitoes). However, filarial worms let only transport their asexual larvae to new hosts (e.g. humans), in which they develop and reproduce in the sexual stages (adult male and female worms).

The life cycle of parasites mostly includes only one type of **final host** (e.g. carnivores), while mostly several types of **intermediate hosts** become involved (e.g. small crustaceans, fish). However, in the case of the species of the genus *Caryospora*, two very different final hosts may be involved, since the sexual process (=formation of oocysts) occurs as well in the intestinal cells of the **primary final host** (snakes) as well as inside their preys (rodents), which thus become **secondary final hosts**. If such hosts are ingested by dogs, oocysts may in addition develop inside their epithelial cells. Thus it can be stated that this parasite is very unspecific with respect to its hosts, but thereby it increases considerably its chances for propagation and thus for survival.

In a broad spectrum of meat feeding hosts – especially in cannibals ingesting meat of their own species – some parasites exist, which use these animals as well as final as intermediate hosts. Thus in some *Sarcocystis* species, lizards may have at the same time tissue cysts as well sexual stages in intestinal cells. The same occurs in cats infected by *Toxoplasma gondii* or in the case of *Trichinella spiralis*, where, e.g. adults may occur in the intestine of pigs and later asexual larvae inside their muscle cells.

The **propagation** of parasites in a given region among peculiar hosts is furthermore supported by the help of further host types, which, however, may also act as final or intermediate hosts at the same time:

1. **Reservoir hosts**

   These are vertebrate hosts such as dogs and rodents, which, in the case of human leishmaniasis, harbour parasite stages which can be transmitted through bites of sandflies back to humans. On the other side, in the case of the agents of human malaria, no further hosts exist.
2. **Transportation host or paratenic host**

   This term describes intermediate hosts wherein no reproduction occurs, but which accumulate parasitic stages, so that these are ingested in high numbers by a final host thus increasing the chance for a successful transmission. Examples are fish containing large numbers of tapeworm stages.
3. **Incompetent host**

   This term describes hosts, wherein an accidentally penetrated parasite cannot develop further on. Examples are the cercariae of various water bird schistosomes in the skin of humans.

1.1 Host Specificity

The above-described host types are based on the varying adaptations of a parasite species at a given host species. This relation may be:

(a) Very **strong**, so that only a single host species is parasitized: e.g. *Isospora hominis* or *Taenia saginata* in humans and *Eimeria maxima* in chicken

(b) Rather **variable**, so that many hosts were used: e.g. *Cryptosporidium* species, many trematodes or most blood-sucking ectoparasites

(c) **Different** in the host types: e.g. in *Toxoplasma gondii*, only felids act as final hosts, while practically all warm-blooded animals may serve as intermediate hosts

1.2 Ontogenetic Development of Parasites

The development of parasitic species may occur in different manners:

(a) **Directly** (i.e. without reproduction) via different larvae looking rather similar to the adult stage (e.g. by **metamorphosis** in the case of some insects or nematodes).

(b) **Indirectly**, i.e. by inclusion of different reproduction processes (e.g. in the case of coccidians, digenetic trematodes), where different generations follow each other. This follow-up of different generations may occur **obligatory** (e.g. in *Sarcocystis* species, digenetic trematodes) or **facultatively** (e.g. in the case of *Strongyloides* nematodes).

1.3 Follow-Up of Different Generations

In the case of many protozoan species, a so-called primary follow-up of generations has been developed, since due to cell divisions, an enlargement of the numbers of individuals occurs, while in the case of metazoans, cell reproduction only increases the body size of the individual organism. Only by partial division of the whole body a new generation occurs. Thus this process is called **secondary follow-up of generations**. A typical **primary follow-up of generations** occurs among coccidians comprising **a sexual generation** and one or several **asexual generations**. The **secondary follow-up of generations** occurs in two different ways:

(a) **Metagenesis**

Here occurs the follow-up of one (or several) asexual generation and a sexual one (e.g. *Echinococcus* species).

(b) **Heterogony**

This term describes the follow-up of a single-sexual (female, parthenogenic) and a typical two-sex (i.e. male/female) generation (e.g. *Strongyloides stercoralis*).

Since rather few informations are available concerning sexuality and chromosomal equipment of many parasites, the determination of many life cycles is difficult (e.g. in trematodes). In addition it occurs that the larvae of several parasites may immediately reach maturity – a phenomenon, which is called **neotenia** (e.g. in Monogenea). Another similar phenomenon is **polyembryony**.

The parasitic worm may be mono- or dioecious. However, in most dioecious species, their sperms mostly reach maturity before eggs. This helps to avoid self-infertilization, which, however, is common in large tapeworms such as *Taenia solium* or *T. saginata* inside the intestine of humans.

1.4 Speed of Development

The larval development of **ectoparasites** depends on the local temperature, while in the case of **endoparasites**, host defence reactions may have considerable influences limiting on growth and ability to reproduce. Thus even in the same species, such processes may need a range from a few days until months or even years. The period, which is needed by a parasite to reach maturity (and production of transmittable stages), is called **prepatent period**. The following period until the end of the production of transmittable stages is named **patency**. The **patent period** of a parasitic species is always species specific and may last a few days (e.g. Coccidia) or even years (e.g. *Taenia* species, large filariae such as *Onchocerca volvulus*). The period between **infection day** and the first occurrence of clinical symptoms is termed incubation period (Latin: incubate = embedding). This period may be short (e.g. hours in case of amoebiasis) or even years (e.g. echinococcosis, schistosomiasis, filariasis). A very important point is reached, when the incubation periods need longer than the prepatent ones. This implicates that a human host does not know that he/she is already able to infect other persons, since he/she is not aware of his/her individual infection. This is, for example, the case in the transmission of the West Nile Virus disease in cases of transmission by clinical blood transfusion or by mosquito bites.

1.5 Adaptations

Ectoparasites have developed peculiar mouth parts and digestion systems in order to obtain and digest the food taken from their hosts. Often they are also using the help of a broad spectrum of **endosymbionts**.

Endoparasites, however, have to solve several more problems. They must develop:

- Sophisticated invasion mechanisms
- Techniques of anchoring themselves inside a host
- Mechanism to protect their progeny inside the host organs
- Mechanism to place their eggs/larvae inside their hosts at places from where they may reach outside places and thus have the chance to become transmitted to other hosts

(a) **Invasion mechanisms**

The infection of a host by an endoparasite may occur **passively** by **oral uptake** of persistent stages such as oocysts, eggs, cysts or tissue cysts, by means of an **injection** process using ectoparasites as vectors or **actively** by the use of own enzymes that enable them to pass the body surface (e.g. miracidia larvae of trematodes or larvae of nematodes).

(b) **Attachment and food uptake**

Parasites have developed a large amount of sophisticated structures, which help their attachment and fixation at inner and outer host tissues and thus make them able to take up food. Examples of organs for fixation are hooks, thorns, claws, suckers or bulbous like magnifications of the cuticle. Food uptake of metazoans is in general done via an intestinal system, which might be subdivided into different activity regions or not. However, several intestinal worms (e.g. cestodes, acanthocephalans) are able to take up all needed substances via their own surface layers, which even morphologically look similar to the surface of the intestines of vertebrates. Protozoans take up their food by the help of peculiar cytostomes or just via vesiculation at the surface.

(c) **Protection from host influences (immune-evasion)**

Endoparasites which live in the intestines of their hosts have to protect themselves from the host's digestive fluids. This is done in many parasitic species by the help of a layer of mucopolysaccharides, which form together with other chemical compound a very resistant **surface coat**, the composition of which is very often changed by the parasite so that its chances in the "fight for survival" become considerably enhanced. Thus this permanent change of the antigenic components at the surface helps that the parasite remains undetected by the host defence system (=**eclipse**), which produces constant antibodies/immuno-globulines (e.g. IgE, IgG, IgM) besides unspecific phagocytic and lytic cells.

Many parasites developed as peculiar protection of their surface the so-called molecular mimicry, which is based on the inclusion of host-derived components into their surface (e.g. seen in schistosomes, filarial worms, *Fasciola hepatica*, etc.). Other parasites interrupt or reduce the formation of the host's MHC-complex (major **histocompatibility complex**). Again other parasites settle in host tissues, which have a low immune-activity such as brain, where tapeworms settle very often. This phenomenon of targeting host organs with low immune-reactivity is described as **sequestration** (Latin: *sequestratio* = separation). Since the above-cited systems are rather rough methods to escape host's immune defence, some parasites have developed further methods. Thus some block or suppress completely the activity of the host's defence system by production and excretion of large amounts of antigenic material which binds the limited number of antibodies produced by the host, so that, e.g. in the case of trypanosomes inside the host's blood vessels, they are able to survive. In another approach some trypanosomes set such a strong stimulus to produce antibodies that this system becomes exhausted and thus at least several trypanosomes may survive.

As soon as (by any many possible reasons) the immune system of a host is exhausted, the so-called opportunistic agents of disease may overwhelm the defence system of the host completely and endanger its life. This phenomenon mainly occurs as soon as the host defence system is weakened by another agent of disease (e.g. in cases of infections with *Cryptosporidium* species or *Pneumocystis jiroveci*).

Nematodes and larvae of insects protect themselves inside host tissues by the help of their **cuticle**, which can be exchanged from time to time, so that host defence systems have problems to detect them. Other parasites protect themselves inside host tissues by formation of so-called tissue cysts (e.g. *Sarcocystis* species, *Trichinella spiralis*, *Onchocerca volvulus*). In many cases the parasites overwhelm the host cells intensely that the host cells appear completely different from the uninfected ones. Furthermore some parasites, which enter cells, which normally have finished their division process, stimulate these cells to new repeated divisions and thus increase the propagation chances of this parasite. This is, for example, initiated by *Theileria* species inside their host cells (lymphocytes of cattle).

(d) **Host specificity**

This phenomenon is only poorly understood: why are some parasites able to develop in different hosts and other species not. Some studies dealing with the metabolism of parasites may perhaps contribute to the above-cited phenomenon. One reason might be that many parasite worms have lost the ability to produce lipid complexes de novo. Thus the host specificity may depend on the lipids that they need and get from their hosts. Other worms which use several hosts may not as specific with respect to their lipid dependence. Such a close dependence is apparently not developed with respect to the use of carbohydrates and proteins, which derive from rather simple, nonspecific molecules.

(e) **Brood protection**

The successful parasite is able to protect its progeny not only from the aggression of the host's defence system, but also outside of the body. This is, for example, done by the development of thick shells around eggs. Furthermore it is needed to depone their progeny in a parasitized body at places, from where the young generation has the chance to get out of the host's body. For example, schistosomes depone their eggs in blood vessels either close to the urogenital or intestinal blood vessels or *Paragonimus* trematodes place their eggs close to blood vessels of the host's lungs and thus enable the eggs to become excreted either with sputum (saliva) or feces or their hosts.

1.6 Pathogenicity

Parasites may harm their hosts in many ways:

- Cells and organs may become destroyed mechanically (e.g. *Plasmodium* spp., *Onchocerca volvulus*, *Ancylostoma duodenale*).
- Host tissues are stimulated to grow to an unphysiological size or tumour development is induced (e.g. in cases of liver flukes, schistosomes).
- Peculiar compounds are extracted from hosts (e.g. vitamin B12 extraction by *Diphyllobothrium latum*).
- Intoxications are induced by discharge of own metabolic excretions (e.g. *Trypanosoma cruzi*, *Plasmodium* stages, ticks).
- Introduction of secondary infections due to bacteria glueing on the surface of parasitic stages (e.g. *Entamoeba histolytica*, surface of nematodes).
- Inoculation of agents of diseases during blood meals of insects and ticks.

1.7 Diseases

The effects of parasites and their clinical importance depend on several factors. One of them is the so-called virulence (Latin: *virulentia* = bad smelling). Host-adapted parasites lead in general only to low-graded diseases, while rather freshly introduced parasite may induce severe diseases. However, any parasitosis starts with an **acute phase** showing significant and severe symptoms, which after activation of the immune systems become reduced and this initiate the so-called chronic phase, which often ends in an **asymptomatic phase**.

The term **zoonosis** describes a disease which is initiated by a parasite, which is an animal. More precise, however, are the terms **anthroponosis** and **zooanthroponosis**. While **anthroponosis** describes diseases, the agents of which are transmitted from humans to other humans (e.g. *Enterobius vermicularis*), **zooanthroponosis** points on diseases, which are based on infections originating from parasites, which have their main host spectrum in animals (e.g. toxoplasmosis, infections with *Trichinella spiralis*). A peculiar and very important form of the **zooanthroponosis** has its origin in the transmitting activity of mosquitoes and/or ticks leading to so-called tick-borne diseases or to **mosquito-borne diseases. Cyclic transmission** occurs when a parasite proceeds a development inside a blood-sucking vector (e.g. in cases of malaria, filariasis, trypanosomiasis), while **direct transmission** describes cases, when, e.g. flies transport worm eggs or bacteria onto lips of humans/animals or when blood-sucking insects have parasite-contaminated mouthparts and detach these parasites onto lips of hosts or into wounds.

1.8 Parasite Diagnosis

The very complex host-parasite relations cannot be depicted in this small volume of important parasite-derived infections. However, some relations should be at least mentioned, especially those which are based on immune reactions or on fecal enrichment essays (for details see in the different chapters).

Indirect Methods
- Complement-binding reaction (CBR)
- Indirect immunofluorescence test (IIFT)
- Indirect haemagglutination test (IHAT)
- Radioimmunoassay (RIA)
- Enzyme-linked immunosorbent assay (ELISA)

Direct Methods

1. **Examination of blood**
   - (a) **The "thick drop"**: A drop of blood is spread out not too thinly over an area about the size of the thumb nail on a clean slide that has been freed as far as possible from grease and is dried in the air. Then it is placed for 5–10 min into ordinary water in a dish to eliminate the haemoglobin.

     Freshly drawn blood is haemolyzed in only a few minutes; it is recommended that, if circumstances permit, a few drops of acetic acid should be added to preparations older than 3 weeks; when this is done, the acid must be removed ("neutralized") by, for example, tap water, before the slide is stained. After the removal of the haemoglobin, the slide is stained (without fixation!) with Giemsa solution: The blood smear is covered with the Giemsa solution (stock solution 1:20 diluted with water) for 30 min. Then the stain is washed off with distilled or buffered water or, in emergencies (if necessary), with rain water. Afterwards the slide is dried in the air (not between filter papers!).

     Important rule: use neutral water, pH 7.0. Use either twice-distilled water (aqua bidestillata) or Weise's original buffer solution, according to the instructions.
   - (b) **The blood smear** (this staining method can also be used for smears taken from organs): A drop of blood, not too big, is smeared onto a clean glass slide with a cover glass, proceeding as follows:
     1. Fixation of the air-dried smear for 3 min in methyl alcohol.
     2. Drying in the air (not between filter papers!).
     3. Staining with Giemsa solution (for each smear five drops of the stock solution to 5 ml of neutral or buffered distilled water), stain for 30 min.
     4. Wash off the stain solution with a brisk stream of water and then allow to dry.
     5. Examine these slides with the oil immersion lens only! When filariae are suspected, it is better to examine the smear with a dry lens after the smear has been covered with a layer of oil. For examination for microfilariae, it is better to use Delafield's haematoxylin rather than Giemsa.
2. **Examination of the stool for intestinal protozoans**
   - (a) **The fresh stool preparation**: Mix a fresh sample of the stool, about the size of a lentil and still as warm as possible, with a drop of physiological salt solution, and cover it with a cover glass and examine in a moderate magnification (400–500×). The motile, vegetative stages of intestinal flagellates are indeed easily found in this way.
   - (b) **Staining with iodine**: Amoebic cysts and their nuclei can be well identified after the addition of 4 % Lugol's iodine to the fresh stool sample.
   - (c) **The stained preparation (by Heidenhain's method)**: Smears are made either on a slide or on three to four cover glasses and are, while still moist, fixed for about 20 min in sublimate alcohol. The preparations are then treated (without allowing them at any time to dry) as follows:

    1. For about 30 min in iodine alcohol (70 % alcohol and tincture of iodine or a brownish Lugol's solution).
    2. At least 1 h in 70 % alcohol.
    3. A brief wash in water.
    4. Mordanting for 1 h in 4 % solution of ammonium ferric alum (dissolve its violet crystals only in distilled water).
    5. A brief wash in water.
    6. Stain for 1 h in Heidenhain's haematoxylin (1 g haematoxylin in 10 ml 96 % alcohol and 90 ml distilled water; the solution must stay in contact with the air for at least 4 weeks!).
    7. A brief wash in water.
    8. Differentiate by washing the preparation for 1–4 min in 2 % ammonium ferric alum solution.
    9. Wash for at least half an hour in running (tap) water.
    10. Pass through the series of alcohols and mount in balsam.

3. **Examination of stools for worm eggs**

   When a worm infection is suspected (e.g. with *Ascaris*, *Enterobius*), the fresh stool should be examined for whole worms that have spontaneously passed out. In tapeworm infection single and usually "motile", segments of chains of these may appear, and these are macroscopically visible. If, on the other hand, actively motile, microscopic small worms (larvae) are found in a fresh stool sample, it is likely that it is an infection with *Strongyloides stercoralis*.

    1. **Direct examination**: A sample of feces about the size of a lentil is broken down in tap water or physiological salt solution in a thin layer onto a microscope slide and spread out and covered with a cover glass. Microscopical examination at a magnification of 100–200 times! **General rule**: The fecal smear should be thin. In order to make eggs with colourless shells better visible, the stool sample can be broken down in Lugol's solution or 2 % eosin solution instead of water. When examinations for worm eggs are being made, the mucus adhering to the feces should always be also examined microscopically, especially flakes of mucus containing blood.

       Since worm eggs are often scantily present in stools, the following so-called concentrations methods are often used (see under 2–5).
    2. **Common salt concentration method** (suitable only for nematode eggs, especially hookworm eggs): A stool sample about the size of a hazel nut, weighing about 1 g, is broken down in 20 times its amount of a concentrated (saturated) solution of common salt (sodium chloride), which is added slowly. Large particles (e.g. vegetable remains, etc.) are skimmed off the surface. After 20–40 min, the eggs, which rise to the surface of the solution, are taken off with a rounded wire loop bent at a right angle (about 1 cm ø). Several of the films of fluid which thus adhere to the loop are transferred to the microscope slide. Microscopical examination should be done at magnifications of 100–200 times.

3. **Zinc sulphate concentration**: This is fundamentally the same as the procedure described under 2; amoebic cysts also can be concentrated by the use of a concentrated (saturated) solution of zinc sulphate.
4. **Telemann's concentration method** (a universal procedure for all worm eggs): A sample of feces about the size of a bean is suspended in a beaker in 7 ml of 50 % hydrochloric acid, and, after the addition of the same quantity of ether, it is stirred until a homogeneous emulsion is formed; the mixture is then poured into a tube, with the aid of a funnel, through a wire gauze sieve (1 mm mesh) or through two layers of muslin, into a centrifuge tube, and is centrifuged for 1 min. Four layers are then formed on it: the uppermost is a yellowish zone of ether; below this is a plug of detritus and the zone of hydrochloric acid and at the bottom is a small sediment, which contains the eggs together with pieces of muscle and cellulose. (**Caution!** With ether there is a risk of explosion!) This sediment is drawn off with a pipette onto a microscope slide and is, after it has been covered with a cover glass, examined.
5. **Concentration by the M.I.F.C. procedure** (merthiolate-iodine-formaldehyde-concentration): For concentration by the so-called M.I.F.C. procedure, two stock solutions are required:
   (a) 250 ml of distilled water, 200 ml tincture of merthiolate No. 99 "Lilly" 1:1000; 25 ml of concentrated formalin, 5 ml of glycerine (=480 ml of the M.F.-stock solution A)
   (b) Freshly made Lugol's iodine solution, not more than 3 weeks old (solution **B**). (Keep both solutions in brown flasks!):
      1. Immediately before starting to work on a stool sample 2.35 ml of stock solution **A** is mixed with 0.15 ml of solution **B**.
      2. A stool sample about the size of a hazel nut is stirred up with the same volume of the mixture of **A** and **B**. The stool sample fixed and stained in this manner is passed through a double gauze filter and transferred to a centrifuge tube with 4 ml of ether. This mixture is vigorously shaken; after the shaking no more ether should remain on the surface. The centrifuge tube is allowed to stand for 2 min and then is centrifuged for 1 min at 1600 revolutions. The plug of detritus between the ether and M.I.F. zone is lightly removed from the tube with the aid of a small rod, and the fluid part is poured off. The worm eggs and also the cysts and vegetative forms of protozoans are found at the bottom of the tube. (**Caution!** With ether there is a risk of explosion!)

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Which Parasites Are Important for Humans?

2

2.1 Groups of Parasites

The selected parasites here belong mainly to a few groups inside the animal kingdom:

(a) **Protists/protozoa**

Unicellular organism and reduced specimens of different origins

(b) **Helminths**

Worms, which belong to the animal phyla: **Platyhelminthes** (flatworms), **Nemathelminthes**, **Aschelminthes** (roundworms), **Acanthocephala** (thorny-headed worms), **Annelida** (e.g. leeches) or **Pentastomida** (tongue worms). The members of these different worms range in a size from a few millimetres up to 30 m.

(c) **Arthropoda**

The name comes from a Greek term and means "feet with segments". This worldwide distributed group includes subgroups such as Chelicerata (=*Greek*: horny claws, e.g. spiders), insects (=*Latin*: animals with a clearly segmented body, e.g. beetles, mosquitoes, bugs, etc.) and Crustacea (=*Latin*: animals with a hard body cover, e.g. shrimps, etc.). All members of these groups are characterized by a rather thick body cover containing chitin and often in addition lime components. All this together forms a stiff exoskeleton, the segments of which are interconnected by smooth ligaments thus guaranteeing flexibility. The specimens of this group harm their hosts either directly, e.g. by their sucking activity or by transmission of agents of diseases (viruses, bacteria, fungi and/or other parasites).

The exact definition of the systematic position of parasites is very difficult, since the members of the different groups have developed often very sophisticated adaptations, so that even members of the same group may appear and behave completely different. Thus this book considers and presents each group of parasites not in a systematically sense, but just under their morphological

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appearance as protozoa, helminths or arthropods and describes their parasitological effects as agents of diseases.

Thus the below-listed simplified system gives just a short overview on the distribution of parasites among different groups of animals and humans and does not reflect the recent sophisticated systematic discussion on interrelations.

Kingdom: Animalia (animals)

Subkingdom: Protozoa/Protista (unicellular stages)
- Phylum: Sarcomastigophora – some parasitic species
- Phylum: Opalozoa – commensals/parasitic
- Phylum: Apicomplexa – many parasitic species
- Phylum: Microspora – parasitic
- Phylum: Myxozoa – multicellular stages, but looking like protozoa, parasitic
- Phylum: Ascetospora – parasitic
- Phylum: Ciliophora – some parasitic species

One of the modern systematics classifies the groups of Apicomplexa (Sporozoa), Dinoflagellata and Ciliophora into the new phylum Alveolata.

Intermediate group: Mesozoa – parasitic, e.g. reduced helminths

Subkingdom: Metazoa (multicellular organisms).
- Phylum: Platyhelminthes (flatworms)
  - Class: Turbellaria – free living
  - Class: Trematodes – parasitic
  - Class: Cestodes – parasitic
- Phylum: Nemathelminthes/Aschelminthes (roundworms)
  - Subphylum: Nematodes (thread worms) – some parasitic species
- Phylum: Acanthocephala (thorny-headed worms) – parasitic
- Phylum: Pentastomida (tongue worms) – parasitic
- Phylum: Annelida
  - Class: Polychaeta – free living
  - Class: Clitellata (leeches) – parasitic
- Phylum: Arthropoda – several parasitic species
  - Subphylum: Chelicerata (ticks, mites) – parasitic
  - Subphylum: Branchiata (Crustacea) – some parasitic species
  - Subphylum: Tracheata (insects) – many parasitic species

2.2 Organs of Humans and Their Typical (Common) Parasites

Localization	Parasitic stages
Lumen of intestine and feces	Cysts of amoebae
	Giardia
	Isospora oocysts
	Caryospora oocysts
	Sarcocystis oocysts
	Cryptosporidium oocysts
	Balantidium cysts
	Microsporidian cysts
	Blastocystis cysts
	Worm eggs
	Larvae of worms
	Adult worms
Wall of the intestine	*Entamoeba*, magna forms
	Giardia trophozoites
	Isospora stages
	Cryptosporidium stages
	Sarcocystis stages
	Caryospora stages
	Balantidium trophozoites
	Microsporidian stages
	Adult trematodes
	Adult cestodes
	Hookworms
	Anisakis worms
	Trichuris worms
	Gnathostoma worms
	Acanthocephalan stages
	Pentastomid stages
Lungs	*Pneumocystis carinii* stages
	Paragonimus worms
	Schistosoma granulomes, adult worms
	Capillaria stages
Saliva	*Pneumocystis jirovecii* stages
	Eggs of lung trematodes
	Echinococcus hooks
	Nematode larvae
	Trichomonas mouth species
	Entamoeba species
Brain	Facultative amoebae
	Cysts of amoebae
	Toxoplasma gondii
	Encephalitozoon stages

(continued)

Localization	Parasitic stages
	Cysticercus of tapeworms
	Larvae of nematodes
Fluid	*Trypanosoma* species
	Amoebae
	Toxoplasma gondii zoites
	Angiostrongylus cantonensis
Lymphe, lymph nodes	*Leishmania* stages
	Toxoplasma gondii zoites
	Filarial larvae
Blood	*Trypanosoma* stages
	Leishmania stages
	Plasmodium stages
	Babesia stages
	Schistosoma larvae, adults
	Dirofilaria stages
	Filarial larvae
	Angiostrongylus stages
Subcutaneous tissues	*Loa loa* stages
	Onchocerca volvulus stages
	Dracunculus medinensis stages
	Mansonella stages
Inside skin	*Leishmania* stages
	Onchocerca stages
	Mites
	Sand fleas (*Tunga*)
On the skin surface	Mosquitoes
	Flies
	Midges
	Simuliids
	Tabanids
	Fleas
	Lice
	Bugs
	Mites
	Ticks
	Leeches
	Vampire bats
Eye	*Acanthamoeba* stages
	Loa loa worms
	Onchocerca volvulus larvae
	Philophthalmus species
	Thelazia species
	Microsporidian stages

(continued)

Localization	Parasitic stages
	Larvae of tapeworms and trematodes
	Pentastomids
Nose	*Leishmania* species
	Amoebae
	Microsporidia
	Fly larvae
	Pentastomid worms
Spleen	*Leishmania* species
	Toxoplasma gondii
	Filarial larvae
Bone marrow	*Leishmania donovani*
	Trypanosoma cruzi
	Toxoplasma gondii
	Microsporidia
Genital- and excretion organs	*Trichomonas vaginalis*
	Microsporidia
	Schistosoma eggs
	Microfilariae
	Dioctophyme renale stages
	Enterobius vermicularis
	Fly maggots
	Vampire fish
Muscles	*Toxoplasma gondii*
	Trypanosoma cruzi
	Sarcocystis species
	Cysticerci of tapeworms
	Trichinella species
Liver	*Plasmodium* stages
	Abscesses of *Entamoeba histolytica*
	Fasciola hepatica
	Dicrocoelium dendriticum
	Clonorchis sinensis
	Opisthorchis species
	Schistosoma granulomes
	Echinococcus cysts and abscesses
	Larvae of nematodes
	Pentastomids

Attention: Many other parasites may be found accidentally in any through-blooded organ!

Protozoans Attacking Humans

3

3.1 History and Relations

The knowledge on the origin of living organisms on earth has been considerably enlarged during the last 20 years, since a broad spectrum of molecular biological methods have been developed or ameliorated. Nevertheless many problems remain unsolved and most of the criteria for the classification of organisms remain weak and are as intensively discussed that nearly every month, new proposals are published, which solve some existing systematical problems, but also give rise to new ones.

However, the (as fixed believed) dogma considering the separate systematic positions of unicellular plants and animals has been “mashed”, so that the former kingdoms “Animalia” and “Plantae” no longer exist as the following term groups:

- Animalicula (van Leeuwenhoek 1676)
- Archaezoa (Petry 1892)
- Protozoa (Goldfuß 1818)
- Protoctista (Hogg 1861)
- Protista (Haeckel 1866)
- Many other recent proposals

Although the origin of the first **Eukaryota** (organisms with a defined cell nucleus) is not yet fully understood, many researchers see good reasons that the Eukaryota of our days have their origin in the repeated fusion of the so-called prokaryotes. Thus it is claimed that in formerly separately existing structures such as mitochondria, peroxisomes and hydrogenosomes, nuclei are penetrated in other “cells” and stay since then together in a status of a permanent **symbiosis**. After these fusions many adaptations occurred, so that today many structures are considered as convergent and are not really an expression of a relationship.

The group of the “true” protozoans contains (living organisms, which have included all functions needed for life (food uptake, metabolism, excretion,

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reproduction, sensitivity, motility, etc.) into the interior of a single compartment (cell) limited by at least one typical bilayered cell membrane. The protozoans possess as typical Eukaryota one or several nuclei. **Polyploidy** may occur; however, the occurrence of several nuclei within a single cell is mostly restricted to rather short phases of the life cycle. These unicellular organisms are limited by a typical cell membrane. The included cell organelles (mitochondria, endoplasmic reticulum, Golgi apparatus, ribosomes, vacuoles, basal apparatus, centrioles, axonemes, flagella, cilia, lysosomes, microtubules, filaments, nucleus, etc.) may appear differently in the different species of protozoans always being adapted at the needed functions. Due to these differences, species diagnosis is possible and free-living stages can be differentiated from parasites. The latter may occur in very large numbers and thus may endanger the health of potential hosts or may even kill them.

However, the existing parasitic protozoans today had been urged to develop strategies and morphological adaptations to survive inside and outside a host when lurking for transmission. Thus today no parasite species is really comparable to another, not even to the much related ones living, e.g. in animals close to humans. Thus the group of protozoan parasites contains a large amount of different organisms, which always need a broad spectrum of sophisticated means to control their attacks.

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3.2 *Trichomonas vaginalis* (Trichomoniasis)

1. **Name**: Greek – *trichos* = tini hair, *monas* = simple creature; Latin, *vagina* = vagina.
2. **Geographic distribution/epidemiology**: Distribution worldwide, especially going along with promiscuity, unprotected sexual intercourse and simultaneous infections with fungi or bacteria. Estimated infections: more than 500 million people. It is the most common nonviral sexually transmitted infection (STI) in the world.
3. **Biology, morphology**: *Trichomonas vaginalis* (Figs. 3.1, 3.2) is a protozoan belonging to the group Flagellata. This parasite measures about 10–25 μm in length and is characterized by a well-remarkable axostyle as well as by four free flagella in addition to one relapsing flagellum reaching only to the middle of the cell. The plasma of the nucleus is homogeneous and invisible in uncoloured and fast-moving trophozoites. This nucleus is situated at the top end of the cell, right under the basis of the flagella. Trichomonads feed on

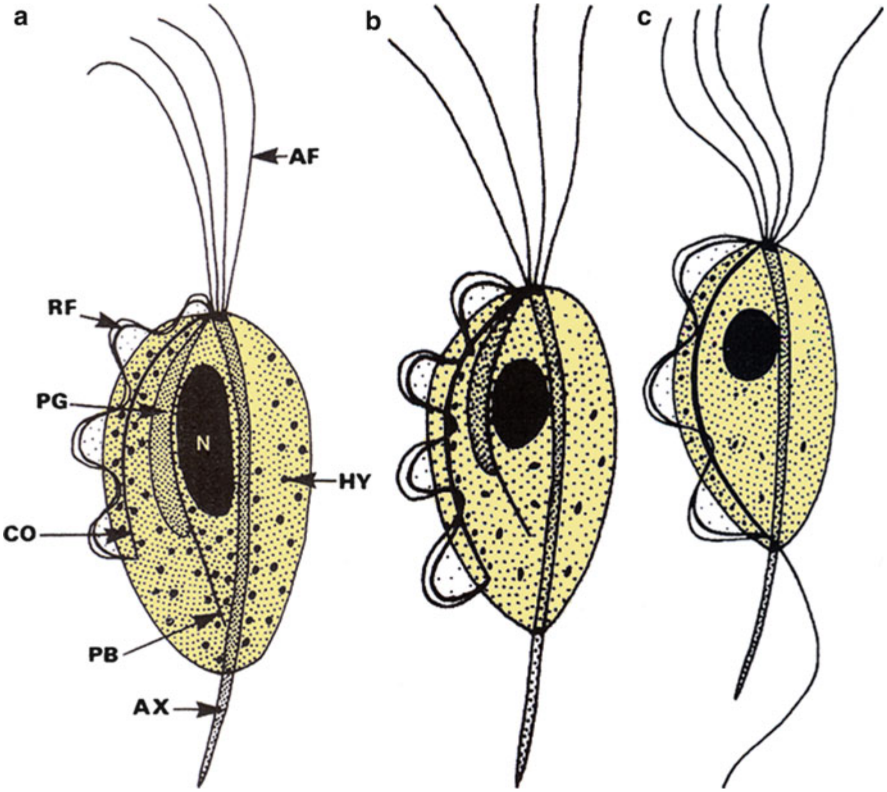

Fig. 3.1 Diagrammatic representations of *Trichomonas vaginalis* (**a**), *Trichomonas tenax* (inside the mouth) (**b**) and *Pentatrichomonas hominis* (in the intestine) (**c**). *AF* free flagellum; *AX* axostyle; *CO* costa; *HY* hydrogenosome; *N* nucleus; *PB* parabasal body; *PG* parabasal body and Golgi apparatus; *RF* relapsing flagellum

bacteria (ingesting them in by phagocytosis) and usually live on the mucosa of the urogenital system of both sexes of humans. Under certain circumstances, which are not well defined yet (changing of pH, occurrence of masses of bacteria or fungi?), *Trichomonas vaginalis* stages start a massive reproduction, dividing longitudinally. Persistent stages like cysts do not occur. The parasite can survive outside the body only for a short time.

4. **Symptoms of the disease (trichomoniasis)**: The incubation time ranges from a few days to several weeks. Most of the infections show no symptoms or go along with a feeling of burning while urinating or frequent urge to do so. In case of infections of females, slimy whitish-yellowish excretions may occur on the mucosa of the vagina. If there occurs a pelvic inflammatory disease, other agents of diseases have to be considered, too. In case of infections of males, the excretion of urine may be blocked partly in the urethra. If prostatitis or

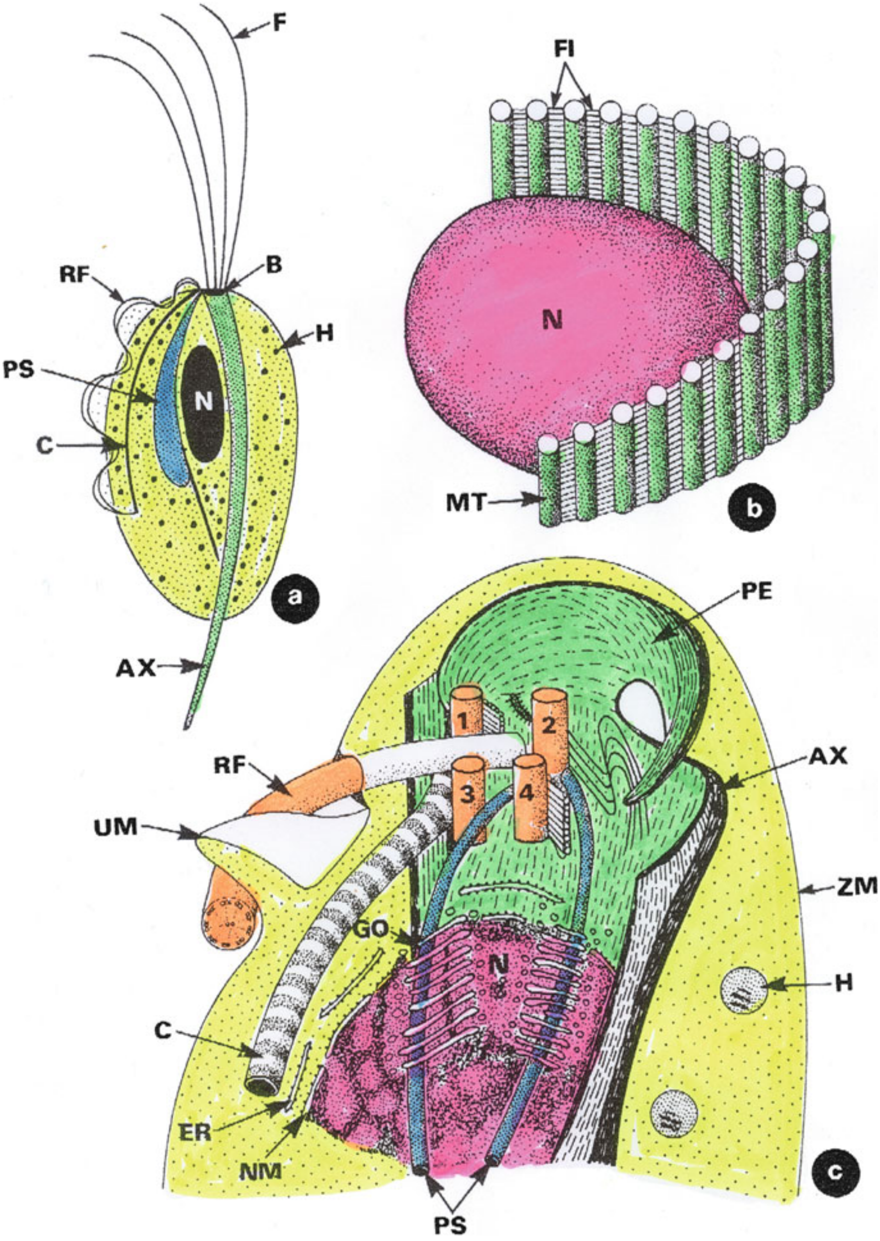

Fig. 3.2 Diagrammatic representation of fine structural aspects of *Trichomonas vaginalis* according to results of Brugerolle (1976). (**a**) Total aspects, (**b**) aspect of the axostyle close to the nucleus, (**c**) apical pole of the cell. One to four basal bodies of the flagella; *AX* axostyle; *B* basal bodies; *C* costa; *ER* endoplasmic reticulum; *F* flagellum; *FI* fibrils; *GO* Golgi apparatus; *H* hydrogenosomes; *MT* microtubules; *N* nucleus; *NM* nuclear membrane; *PE* pelta; *PS* parabasalian strands; *RF* attached flagellum; *UM* undulating membrane; *ZM* cell membrane

epididymitis occurs, other agents of diseases have to be considered, too. Long-time trichomoniasis in males and females may lead to infertility.

5. **Diagnosis**: Freely moving trophozoites may be observed microscopically inside the slimy excretions after dilution in a drop of a 0.85 % NaCl solution or after culturing. The Giemsa-stained coloration shows a blue cytoplasm, while the nucleus, axostyle and the flagella are coloured slightly in red. For the differential diagnosis, it is important to distinguish parasites from leucocytes. Latent infections can be shown by serological methods (KBR, IIFT, IHA, ELISA). They are highly recommended and very successful.
6. **Pathway of infection**: The transmission mostly occurs during sexual intercourse. Trophozoites cannot survive outside the body [especially not in chlorinated water (44 mg/l) of swimming pools]. People should not use tumblers in public swimming pool locations in order to avoid infections of own sexual organs due to contact to infectious remnants of slime of foreign origin.
7. **Prophylaxis**: Avoidance of unprotected sexual intercourse with new partners.
8. **Incubation period**: 4–24 days.
9. **Prepatency**: 4–20 days.
10. **Patency**: Several months to years in cases of lack of hygiene or due to reinfection (ping-pong type) via an infected partner who does not show symptoms.
11. **Therapy**: It is important that both sexual partners must be treated at the same time to prevent a new infection. Often coinfections occur with fungi (e.g. *Candida*) and/or different species of bacteria. Therefore nitroimidazole derivatives (e.g. metronidazole) are highly recommended by using either 2 g as a single dose or (especially in case of therapy failure) 2 × 500 mg daily for 7 days eventually in combination with vaginal suppositories containing metronidazole (100 mg daily). However, treatment failure may range in up to 7–10 % of the cases.

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3.3 Flagellata of the Intestine

A number of mostly nonpathogenic flagellates occur in the colon and caecum of humans. However, as shown in several publications, gastrointestinal disease may occur in children and farm/house animals. All of them produce cysts being excreted in feces. Their number is rather low, so that they can be proven only by the use of enrichment methods (Fig. 3.3):

1. **Species**
    (a) ***Pentatrichomonas hominis***
    Size 8 × 5 μm; four or often five front flagella and one relapsing flagellum with an undulating membrane which does not reach the very end of the flagellum; an axostyle occurs always. It occurs in often high prevalence rates in humans, nonhuman monkeys, cats, dogs, cattle, goats and pigs.
    (b) ***Enteromonas hominis***
    Length 5–10 μm; three free-front flagella and one relapsing flagellum without undulating membrane; an axostyle does not occur.
    (c) ***Chilomastix mesnili***
    Length 6–24 μm; three flagella at the front and one short relapsing flagellum running through a cytostomal channel; an axostyle does not occur.
    (d) ***Retortamonas intestinalis***
    Length 4–9 μm; one front flagellum and one relapsing flagellum, which is protruding from the cytostome; an axostyle does not occur.
    (e) ***Dientamoeba fragilis***
    This parasite will be discussed in Chap. 10.2 in detail.

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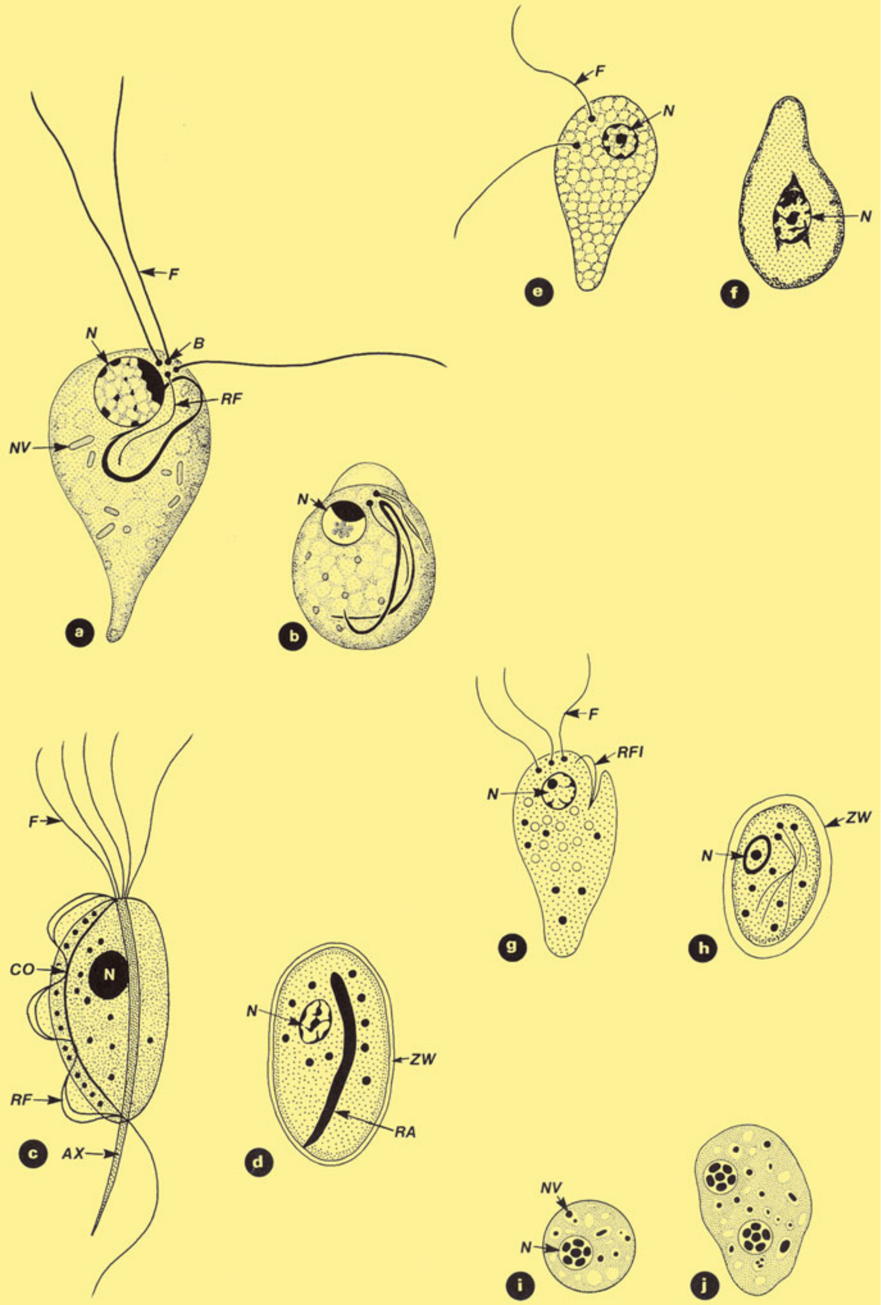
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Fig. 3.3 Schematic representations of the flagellates inside the intestine: (**a**, **b**) *Chilomastix mesnili*; (**c**, **d**) *Pentatrichomonas hominis*; (**e**, **f**) *Retortamonas*; (**g**, **h**) *Enteromonas hominis*; (**i**, **j**) *Dientamoeba fragilis*. *AX* axostyle; *B* basal body; *CO* costa; *F* flagellum; *N* nucleus; *NV* food vacuole; *RA* remnant of the axostyle; *RF* relapsing flagellum; *RFI* relapsing flagellum in invagination; *ZW* cyst wall

3.3.1 *Trichomonas tenax*

1. **Name**: Greek – *trichos* = tini hair, *monas* = simple ceature; Latin, *tenere* = to keep, to stick to.
2. **Geographic distribution/epidemiology**: Worldwide, widely distributed in cases of insufficient mouth hygiene.
3. **Biology, morphology**: *Trichomonas tenax* lives without any cyst production in the mouth of humans and has a length of 5–16 μm. These parasites have four flagella at the front tip and one relapsing flagellum ending nearly in the middle of the cell. The multiplication of the trophozoite occurs by longitudinal division. They feed in the mouth on the bacterial flora as well as on sugar remnants occurring there. They do not survive the passage through the intestine nor can they live in the vagina. But in the mouth, masses of them may occur if mouth hygiene is poor. In such cases infestation rates of more than 50 % are common and cell destruction was noted.
4. **Symptoms of the disease**: There are no severe symptoms; obviously this flagellate is mostly nonpathogenic. However, it was observed in the lung and in the trachea.
5. **Diagnosis**: Microscopic investigation of the dental plaque floated in 0.85 % NaCl.
6. **Pathway of infection**: Orally, using contaminated drinking glasses or kissing of a person with reduced mouth hygiene.
7. **Prophylaxis**: Teeth brushing three times daily.
8. **Incubation period**: Unknown.
9. **Prepatency**: Unknown.
10. **Patency**: Months in cases of lacking mouth hygiene.
11. **Therapy**: Not necessary in case of good mouth hygiene.

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3.3.2 *Entamoeba gingivalis*

1. **Name**: Greek – *enteron* = intestine, *amo* = change, *gingivalis* = belonging to gingiva.
2. **Geographic distribution/epidemiology**: Worldwide, often, but mostly not noted.
3. **Biology, morphology**: *Entamoeba gingivalis* has a size of 5–30 μm and is spread in the gingival and dental plaque of more than 50 % of humans. This

amoeba is characterized by a very distinctive ectoplasm. The chromatin of the nucleus is slightly more even distributed than in the case of *E. histolytica* (Fig. 3.19). The nucleolus is situated in the centre of the cell. Vacuoles with lyophilized leucocytes often occur in the endoplasm, especially in the case of gingival inflammations. *E. gingivalis* amoebae commonly feed on bacteria within plaques. They do not produce cysts and thus they do not survive an intestinal passage. Therefore they have to be transmitted during mouth to mouth contacts.

4. **Symptoms of the disease**: None, although some authors suppose that they might be involved in the formation of maxillodental abscesses. In immunosuppressed persons these parasites may grow up in masses and introduce periodontitis.
5. **Diagnosis**: Microscopic evidence of trophozoites in elutriated (0.85 % NaCl) plaque.
6. **Pathway of infection**: Orally from person to person or by contact to contaminated cups, spoons, etc.
7. **Prophylaxis**: Correct oral hygiene and use of clean dishes/cups.
8. **Incubation period**: Unknown.
9. **Prepatency**: Unknown.
10. **Patency**: Months to years in cases of poor hygiene of the mouth.
11. **Therapy**: Not necessary in cases of adequate mouth hygiene.

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3.4 *Giardia lamblia* (syn. *G. duodenalis, G. intestinalis*)

1. **Name**: This species is named after two scientists: Giardi (1846–1908) and Lambl (1841–1895).
2. **Geographic distribution/epidemiology**: Worldwide, more frequently in the tropics; it is estimated that some hundred millions of humans are affected by this agent of disease. However, severe clear symptoms occur mostly only in persons suffering from immunosuppression. Anton van Leeuwenhoek first detected this parasite in his own stool in 1681. WHO recognized this species only in 1981 as true parasite.
3. **Biology, morphology**: *Giardia lamblia* trophozoites appear microscopically like wind dragons, living in the small intestine of their hosts. The parasites are attached to the microvilli of the mucosa cells with its concave ventral side (Fig. 3.4). The pear-shaped, dorsoventrally flattened trophozoite is about 20 μm

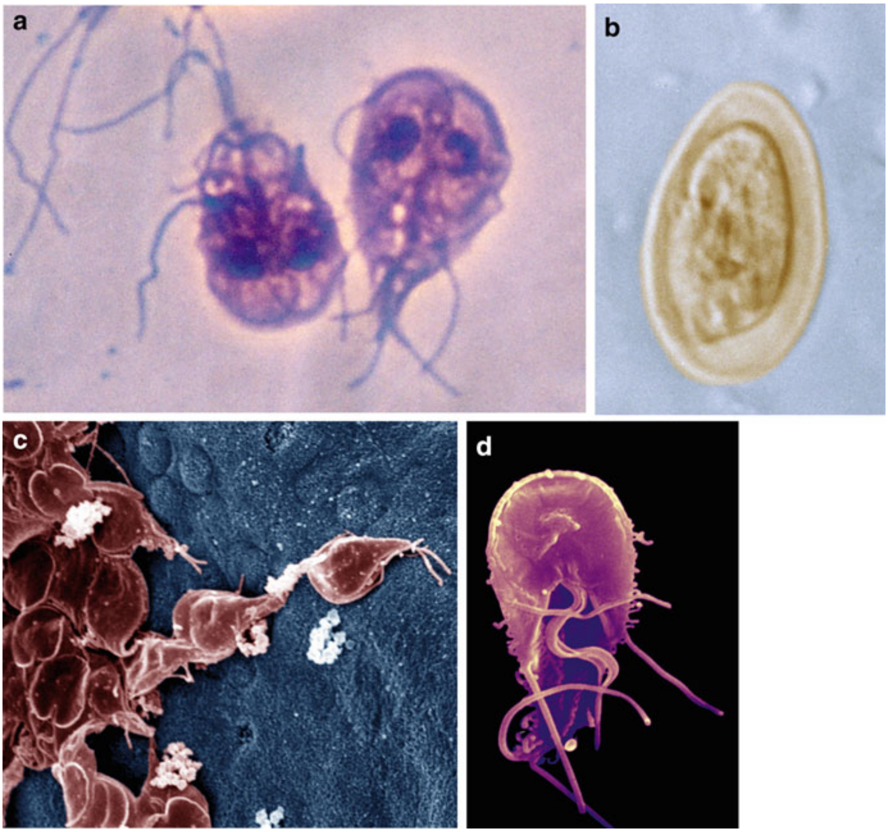

Fig. 3.4 Light and scanning electron micrographs of *Giardia lamblia*. (**a**) Giemsa-stained trophozoites. (**b**) Trophozoite and a cyst with four nuclei. (**c**) Trophozoites attached on microvilli of the intestinal mucosa. At places where trophozoites have been detached, depression marks become visible. (**d**) Ventral portion of a trophozoite showing the big adhesion organ (discus)

long and 7–10 µm wide. It possesses two nuclei of the same size as well as eight free flagella. The multiplication occurs as a longitudinal binary division. *G. lamblia* produces cysts with four nuclei in the final state of the infection after numerous divisions. They are ovoid and measure 10–14 µm in diameter. They are excreted within the feces. Humans and animals are infected by different genotypes. Types A and B occur both within humans and animals. They may become transmitted vice versa. Six further genetic groups (C–H) occur in animals, are host specific and do not infect humans.

4. **Symptoms of the disease (Giardiasis)**: Often the infection runs symptomless. Under certain circumstances, which are not yet totally understood (e.g. other irritations of the intestine, variations of genotype and thus resulting pathogenicity), agent-induced lack of the enzyme disaccharidase of the duodenal mucosa, lacking production of the immune globulin A, T-cell-defects, etc.

may occur. Heavy symptoms may occur after an incubation period of a few days to several weeks: fatigue, vomiting, colics of the bowels, meteorism, flatulence, heavy diarrhoea of partly watery and partly frothy consistence. The feces are not purulent (as they do not contain leucocytes) nor slimy or bloody. Only very seldom blood traits become visible. In the diarrhoeic material/feces, many vegetative stages of *Giardia lamblia* can be found, although they cannot survive outside the body. In case of **chronical infections** (especially in cases of HIV patients or in cases of malnourished children in the tropics), anatomical and functional changes of the mucosa of the small intestine can lead to malabsorption. Malnutrition and symptoms of giardiasis may support severity of the infection. Sometimes invasion of the ductus choledochus occurs. Investigations like probing or contrast filling of the ductus choledochus or ductus pancreaticus can lead to severe inflammations as well as to heavy pancreatitis caused by *Giardia lamblia*. These symptoms often induce retardation of the normal development of infected children. In the case of HIV patients, massive and live-threatening diarrhoeas can be induced by parasitizing *Giardia* stages.

5. **Diagnosis**: The presence of trophozoites can be diagnosed within fresh feces as motile parasites or with the help of a coloured smear preparation (Heidenhain, Trichrome or Lawless coloration). If there is no chance of investigating fresh diarrhoea stools, the fixation of the stool immediately after discharging is necessary (PVA, MIF- or SAF-solution), since otherwise the trophozoites are destroyed. In contrast to trophozoites, the cysts still can be found in those unfixed, older stool probes. Additional cysts can be effectively enriched by MIF- or SAF-enrichment methods. However, the excretion of cysts often varies heavily and can totally be absent in the case of an acute giardiasis with a very fluid diarrhoea. In order to rule out giardiasis, several (minimum of three) stool probes from different days should be investigated in order to find cysts and/or trophozoites. Sometimes the infection can only be detected by the proof of trophozoites from duodenal fluids, which can be obtained endoscopically.

   The importance of immunological tests (IgM- and IgA-antibodies; immunofluorescence tests or the proof of antigens in the stool) is still not yet clear, as well as the efficacy of molecular biological methods such as PCR of the stool probes.
6. **Pathway of infection**: Cysts are taken up orally within contaminated water or food; frequent repeated infections are possible, because there is no immunization so far. Flies can act as vectors. *Giardia* leads to a typical zoonosis, since the parasitic genotypes A and B may occur both in humans and animals.
7. **Prophylaxis**: Cleanliness, avoiding or cooking of potentially contaminated food, boiling of drinking water.
8. **Incubation period**: 2–21 days (mostly 1 week).
9. **Prepatency**: 3–4 weeks.
10. **Patency**: Possibly years.
11. **Therapy**: Oral application of metronidazole (adults, 3 × 400 mg per day for 5 days; children, 15 mg/kg body weight daily for 5 days) or the use of other

nitroimidazoles. The cure rates reach 90 % when using the above-cited compounds. Albendazole (400 mg daily for 5 days) and furazolidone are curing as well. However, a second or even a third drug intake is needed. Controls are needed in case of new infections. All these above-cited substances are forbidden during pregnancy. In such case a symptomatical “treatment” is the method of choice (e.g. drinking of lots of fluid).

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3.5 *Trypanosoma brucei* Group (African Trypanosomiasis)

1. **Name**: Greek – *trypanon* = drill/borer, *soma* = body; Bruce = name of an English scientist, David Bruce (1855–1931).
2. **Geographic distribution/epidemiology**: *Trypanosoma brucei rhodesiense* (East Africa), *Trypanosoma brucei gambiense* (West and Central Africa), hundreds of thousands of cases, with the number of cases increasing recently.
3. **Biology, morphology**: Both species (Figs. 3.5, 3.6) cannot be distinguished morphologically. So-called trypomastigote stages occur in human blood and move freely with the help of their single flagellum. They reach a length of 15–40 μm and are transmitted during the blood meal of the tsetse fly (genus *Glossina*) within the saliva into the human body. These *Trypanosoma* stages can be microscopically identified by their rounded posterior end. The kinetoplast, which appears bluish (in Giemsa stain) and contains large amounts of DNA, represents the anterior portion of the mitochondrium. It can be observed below the basal apparatus of the flagellum (Fig. 3.10). The nucleus can be seen right in the middle of the cell. The surface of the parasite is protected from the attacks of antibodies of the host by a protective layer called **surface coat**, which contains proteins and mucopolysaccharides anchored at the membrane. The composition of the surface coat is a matter of change during each division, which occurs as longitudinal binary fission. The blood stages obtain their energy with the help of an anaerobic glycolysis. Tiny trypomastigote stages may pass the blood-brain barrier and multiply in the fluid as trypomastigote

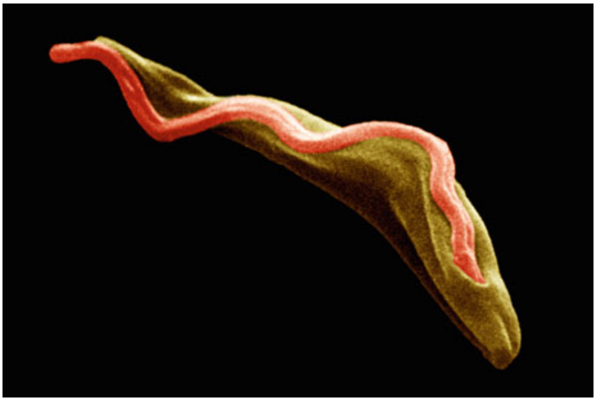

Fig. 3.5 Scanning electron micrograph of a blood stage of *Trypanosoma brucei gambiense* showing the red coloured flagellum originating from a flagellar pocket at the terminal end and stretching along to the surface until the anterior end

stages. Furthermore they can multiply in the brain cells itself as amastigote stages, which possess an extremely tiny flagellum. Some of the tiny blood stages change their shape into stumpy forms while dividing. Only these stumpy stages are able to keep on developing in the tsetse fly after being ingested by the insect during its blood meal. They transform themselves (under divisions) to epimastigote stages in the upper mouth parts and later the intestine of the vector. The epimastigote stages have the flagellar pocket of their flagellum behind the middle of the cell, and the nucleus is situated in front of it. After perforation of the intestine wall, they invade the salivary glands in about 20–40 days. There they multiply and finally transform into infectious trypomastigote stages, which develop the surface coat which protects them from the attacks of the host's antibodies. Besides humans also so-called reserve hosts can be infected, e.g. monkeys, dogs, pigs and antelopes in the case of *T.b. gambiense*. In the case of *T.b. rhodesiense*, goats, sheep, cattle, pigs and several antelope species can be infected, too. The agents of the sleeping sickness of ruminants (the so-called Nagana disease due to *T.b. brucei*) in opposite do not develop in the human blood.

4. **Symptoms of the disease (trypanosomiasis, trypanosomosis)**:
   4.1. **First stage**
      (a) Primary reactions appear as swellings at the biting site, followed by local oedema. They remain visible for about 1–3 weeks due to the massive local multiplication of the parasite. Huge numbers of trypanosomes can be found in the liquid of the oedema.
      (b) Fever (reaching about 39 °C) occurs from 2–4 weeks after infection because of multiplication of the parasites in the circulating blood fluid. During this period the trypanosomes become first visible in blood smears. Therefore this period is called **incubation time**. Fever can last 2–3 weeks, depending on how quick most of the parasites are eliminated by human antibodies. New multiplications of the parasites and their following destruction lead to further fever attacks (up to 41 °C), which however, occur irregularly. They can be accompanied by shivers and chills in the case of *T. brucei rhodesiense*.

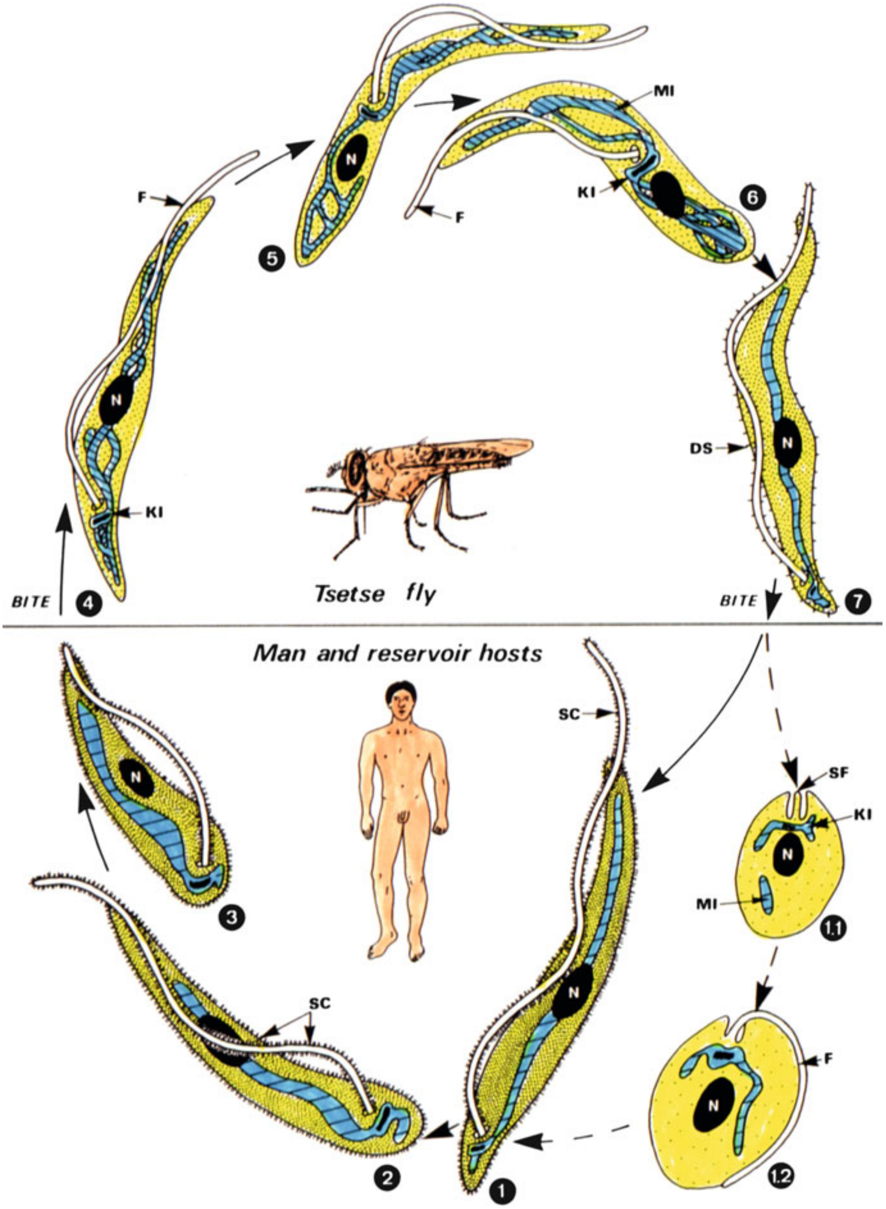
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Fig. 3.6 Life cycles of Trypanosoma brucei gambiense and *T. b. rhodesiense*, causatives of the sleeping sickness diseases in West and East Africa. **1** Slender trypomastigote bloodstream forms (they also penetrate into the cerebrospinal fluid). These stages are characterized by a mitochondrion with sparse, short tubular cristae. The slender forms lack a functional Krebs cycle and cytochrome chain. **1.1** According to several authors, amastigotes (i.e., micromastigotes) are seen 48 h later inside the cells of chorioidea. **1.2** Transformation of amastigotes into sphaeromastigote forms (surface coat not investigated), which give rise to slender blood forms. **2** Intermediate trypomastigotes which reproduce by intensive binary fission; cristae of mitochondrion lengthen. **3**

(c) Lymph node swellings (polyadenitis) occur because the parasites spread over the whole lymph system at the time when the parasites first appear in the blood. Swellings (chancres) in the neck region of the patients are very characteristic during this period. However, in the case of infections with *T. brucei rhodesiense*, lymph node swellings are rare and thus not important as diagnostic signs.

4.2. **Second stage**

The invasion of the central nerve system of humans occurs in *T.b. rhodesiense* about 3 months after infection, while in the case of *T.b. gambiense*, it takes about 9–18 months. However, in both cases brain invasion leads to the formation of a progressing meningoencephalitis, which ends fatal, if there is no treatment at an early date at the beginning of the brain invasion. Therefore it is needed to control whether parasites are present in the fluid, since during this phase of the infection, mostly only a few parasitic stages can be found inside the blood. The untreated final phase of the disease is characterized by a permanent unconsciousness, which led to the trivial description of this disease as *sleeping sickness*. However, in the case of *T.b. rhodesiense*, where the clinical symptoms are much more intense than in *T.b. gambiense*, the typical "sleeping phase" often may be absent, since people die earlier (already after 5–6 postinfection months due to heart damage, e.g. myocarditis).

5. **Diagnosis**: With respect to the bad prognosis for the various symptoms of sleeping sickness and considering the heavy side effects of the available anti-trypanosomiasis compounds, it is very important to verify a "sleeping sickness" as early as possible by proving the presence of typical trypomastigote stages. This can be done by **microscopical examination** of the flagellates taken from the oedema fluid, but also taken from the neck swelling, from blood, from lymph nodes (especially in *T.b. gambiense*) or from bone marrow. In **native preparations** (=not fixed), the parasitic stages can easily be seen due to their twisting movements. **Giemsa-stained smear preparations** show clearly the parasites among the blood cells. However, species determination is doubtful,

Fig. 3.6 (continued) Stumpy trypomastigote forms have a partially functional Krebs cycle but still lack cytochromes. When these stages are ingested by the tsetse fly (*Glossina* spp.), they may develop inside this vector. According to results of Jenni (Basel), bloodstream forms are diploid, and sexual processes with mating and DNA recombination occur inside the vector. **4** Trypomastigotes (without surface coat) in the crop of the tsetse fly. A waiting phase of at least 1 h is needed. **5** Transformation to epimastigote (=procyclic) forms in the cardia and midgut of the tsetse fly, these stages develop a smooth surface coat an divide for about 12 days. **6** Epimastigote forms have a mitochondrion with numerous platelike cristae, acting with an active Krebs cycle and the cytochrome chain. Reproduction occurs by constant binary fission. These stages leave the intestine and enter the salivary glands. **7** Metacyclic trypomastigote from the salivary glands, which develops a blood-stage surface coat (DS) and has a mitochondrion with closely packed tubular cristae. This stage is infectious for man and reservoir hosts when injected during the next blood meal of the vector. The whole development in the vector lasts 25–50 days and each tsetse fly remains infected for life (=2–3 months). The minimum infective dose for man is about 300 flagellates. *DS* developing blood-stage surface coat; *F* flagellum; *KI* kinetoplast; *MI* mitochondrion; *N* nucleus; *SC* surface coat; *SF* short flagellum of amastigotes

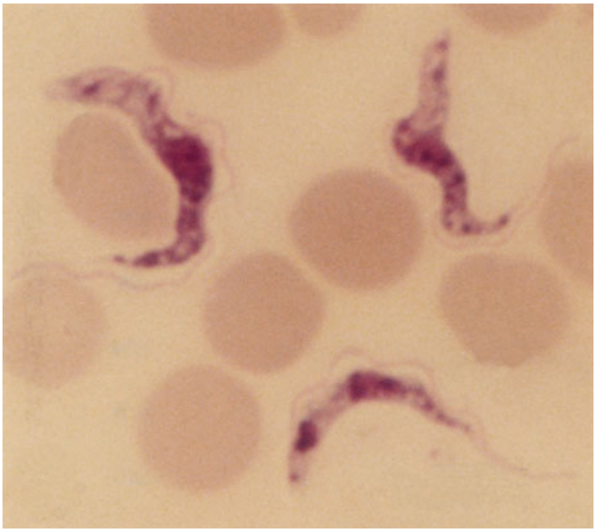

Fig. 3.7 Giemsa-stained blood smear showing slender stages of a person infected with *T.b. rhodesiense*

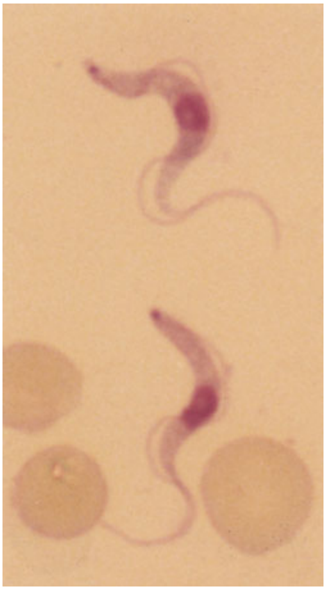

Fig. 3.8 Giemsa-stained blood smear showing slender stages of *T. b. gambiense*

since the blood stages of *T.b. rhodesiense* and *T.b. gambiense* look rather similar. There are **long slender** and **stumpy forms** visible. In the case of *T.b. rhodesiense* and *T.b. gambiense*, the measures of slender forms are 20–35 μm in length (Figs. 3.7, 3.8) and 1.2–2.3 μm in width, while the stumpy forms reach a length of only 19–25 μm. Intermediate forms are also present. The slender forms are able to proceed longitudinal binary fissions, while the stumpy forms apparently do not divide anymore. However, the diagnosis of stages in blood smears remains difficult due to the fact that the numbers of parasites remain mostly rather low. Therefore it is needed to use additional methods:

1. **Microhaematocrit method**

   After centrifugation of blood (5 min at 10,000 g), the parasites become visible due to their movements in the plasma layer which is formed adjacent to the column of red blood cells.
2. **Ione-exchange chromatography**

   This method was developed by Lanham. Hereby the host erythrocytes become retained in a minicolumn being filled with 2–10 ml diethylaminoethyl cellulose, whereas the *Trypanosoma* stages are accumulated (due to their different surface loads) in a phosphate-glucose buffer at pH 8 and may be concentrated by centrifugation. Depending on the volume of the column 0.2–1 ml, blood should be investigated.
3. **Animal infections**

   Especially in the case of *T.b. rhodesiense*, the existence of trypanosomes can be diagnosed when rodents are infected experimentally by intraperitoneal injection of 0.5 ml blood. Trypanosomes would appear after 3–9 days in blood. However, it is also needed to investigate the fluid, which has to be centrifuged (10 min at 9000 g).
4. **Serologic methods**

   Except for the first 10–14 days after the infection, IgG and IgM antibodies can be diagnosed by different test systems (IFT, ELISA, CATT). However, also false (negative) results are possible. A brain invasion was often proven, when the examination showed pleocytosis (>5 cells) and enrichment of proteins (>40 mg/dl).

6. **Pathway of infection**: The infectious stages of the trypanosomes are injected during the blood meal (=salivary infection) of tsetse flies (genus *Glossina*). Both males and females are able to transmit infectious stages. However, only 0.1 % of the flies are infected in endemic regions. It takes 3–5 weeks to become able to transmit the parasites after a tsetse fly has been infected during a blood meal. **Attention**: The agents of sleeping sickness may also become transmitted by blood transfusions.
7. **Prophylaxis**: Avoidance of bites of tsetse flies (*Glossina* species) by the use of repellents (e.g. products containing Icaridin/Saltidin).
8. **Incubation period**: 1–21 days after the bite of an infected tsetse fly, an oedema is produced at the biting site (primary effect). After 3 weeks high fever may start in infections by both *Trypanosoma* species. However, it takes up to 1 year until cerebral symptoms occur after infections with *T.b. gambiense*, whereas in cases of *T.b. rhodesiense*, infections such as cerebral symptoms occur already after 3 months.
9. **Prepatency**: After 1–3 weeks, parasites have been significantly reproduced in the surroundings of the biting site.
10. **Patency**: Eventually years in cases of chronic infections with *T.b. gambiense*. Months in cases of *T.b. rhodesiense*, mostly leading to quick death in untreated cases.

11. **Therapy**
    (a) **West-African sleeping sickness**

    Without treatment this variation of the sleeping sickness leads to death. However, the following treatment scheme has shown good results:

    Phase 1: The use of pentamidine (Company Sanofi-Aventis): 4 mg/kg body weight (max. daily doses 200 mg). Treatment is done for 7–10 days per intramuscular injection.

    Phase 2: The use of melarsoprol of eflornithine; *Melarsoprol*, 10 days 2.2 mg/kg bodyweight. *Eflornithine*: 14 days, 4× daily (=all 4 h) 100 mg/kg bodyweight applied as infusion. This compound is used especially in cases of melarsoprol resistance.

    (b) **East-African sleeping sickness**

    Without immediate treatment this disease remains fatal. Even under treatment about 10–15 % of the patients die.

    Phase 1: Still today the product Suramin® = Germanin® (developed just after the First World War by Bayer, Germany) is the product of choice; a 10 % solution has to be injected into veins (1 g per injection = 20 mg/kg bodyweight) on days 1, 3, 7, 14 and 21. A total maximum of 5 g should not be exceeded.

    Phase 2: The use of melarsoprol (Arsobal®) is still the product of choice. The daily simple dose (3.6 mg/kg bodyweight) should be injected for 3–4 days. Then a nontreatment period of several days should follow. In total 3–4 such cycles should be done. According to the scheme of Apted four series with three applications each and an increase of the dose for 0.5 ml (from 0.5 ml = 0.36 mg up to 5 ml = 3.6 mg) at intervals of 7 days should be done. However, in all cases severe immune reactions may occur so that an additional application of cortisone (e.g. prednisolone 1 mg/kg bodyweight) is needed. Some publications recommend that patients in the second phase of the disease should be treated not only by Melarsoprol® but also additionally with Nifurtimox®.

    Due to the chance of a treatment – although all medicaments are extremely toxic – today sleeping sickness affords rather few deaths per year, although 10,000 humans had been infected in the year 2014 among 50 millions of endangered people. However, in times of local wars, which stop protection campaigns and serial treatments, the death toll may increase very quickly. In times of Robert Koch's expeditions (~1905/1906), millions of Africans were infected and died.

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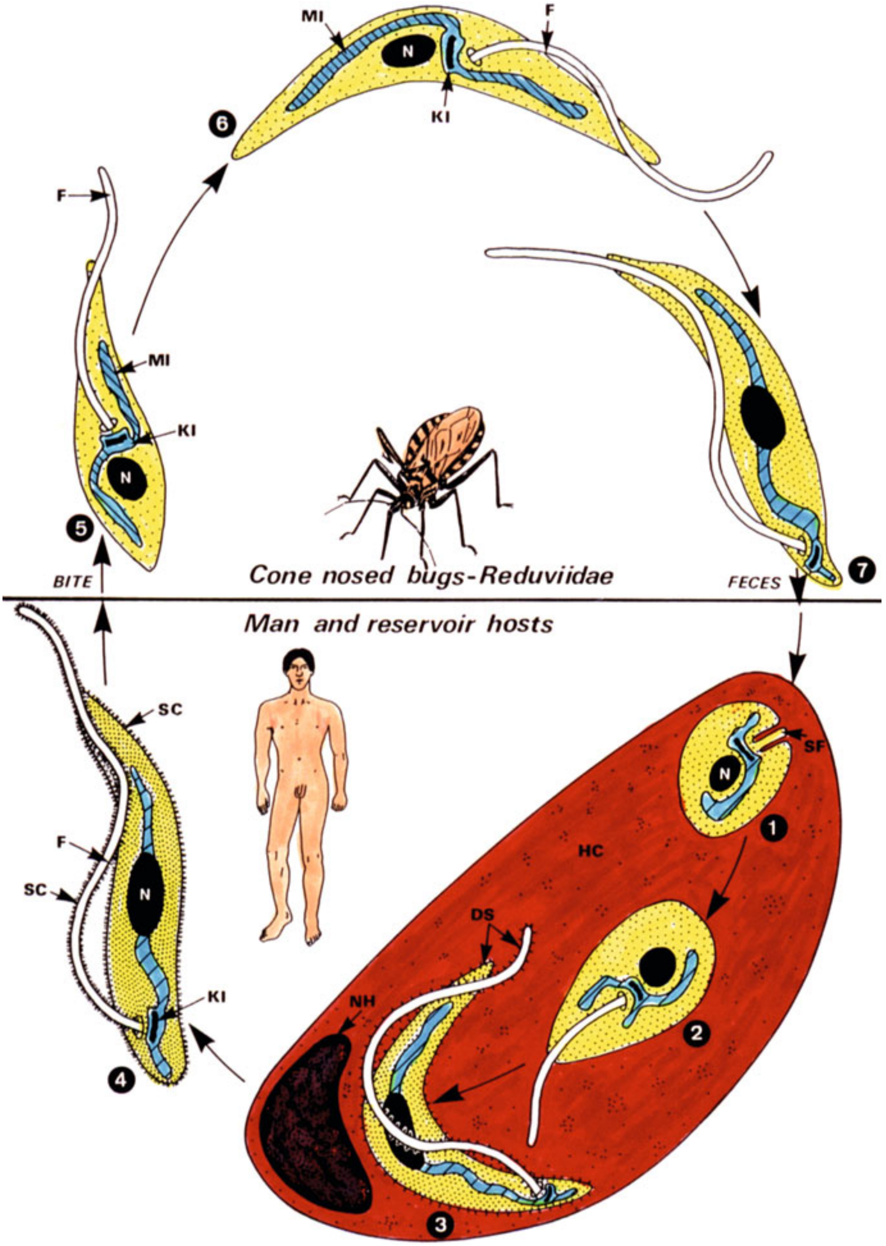
3.6 South American Trypanosomes

3.6.1 *Trypanosoma cruzi* (Chagas' Disease)

1. **Name**: Greek – *trypanon* = drill; *soma* = body. The species name was given honouring the Brazilian scientist Oswaldo Cruz (1872–1917). The disease (Chagas' disease) is named after its discoverer (Carlos Chagas, 1879–1934), a Brazilian physician and researcher.
2. **Geographic distribution/epidemiology**: The agents of disease are distributed from southern regions of the USA, via Mexico and Central America to South America until Argentina and Northern Chile. About 50 million people are infected. However, new infections become reduced due to large bug-control programmes in rural regions.
3. **Biology, morphology**: Humans and a broad spectrum of animals belonging to a sylvatic cycle such as rodents, monkeys, cats, dogs, opossum, armadillo, etc. are infected during blood sucking of reduviid bugs belonging to the genera *Rhodnius, Triatoma, Dipetalogaster*, etc. In contrast to African trypanosomes, the transmission of stages of *T. cruzi* does not occur via injection of saliva of the tsetse flies but occurs when parasites, which are included in droplets of bug feces, are rubbed into the wounds at biting sites of the bugs (Figs. 3.9, 3.10). Then occur in the blood of human's trypomastigote stages, which appear C- or S-like shaped (Fig. 3.10) and reach a length of 15–20 μm. They enter in human macrophages, muscle and nerve cells, where they are situated directly inside the cytoplasm. Penetrated trypomastigotes are transformed into amastigotes (=short mastigotes), which start binary fissions and finally become via epimastigotes again trypomastigotes. Such infected host cells were called **pseudocysts/**


MI
F
N
KI
6
F
MI
KI
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5
BITE
Cone nosed bugs-Reduviidae
FECES
7
Man and reservoir hosts
SC
F
SC
N
KI
4
SF
N
1
HC
DS
NH
2
3

Fig. 3.9 Life cycle of *Trypanosoma cruzi*, cause of Chagas' disease in South America. **1** Amastigotes=micromastigotes reproduce by binary fission inside the cytoplasm of different host cell types (RES, heart muscle, nerve, spleen, liver etc.). Host cells appear as "pseudocysts" when they are completely filled with parasites. **2**, **3** Transformation to trypomastigotes (**3**) via epimastigotes (**2**) and development of a surface coat (DS) occurs inside the cell. **4** Trypomastigotes inside the bloodstream after disruption of the host cell. These stages enter other host cells or are ingested by cone-nosed bugs during the blood meal. **5** Transformation to epimastigotes inside the

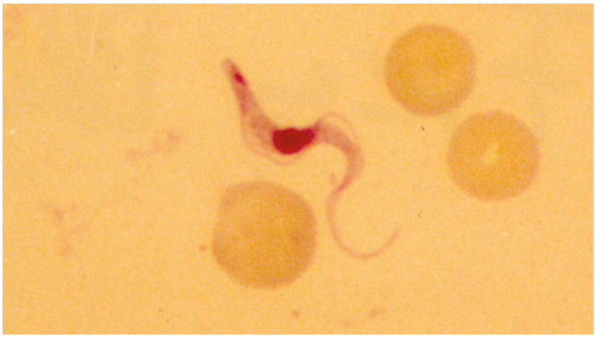

Fig. 3.10 Light micrograph of a trypomastigote stage of *T. cruzi* in a blood smear preparation

(Fig. 3.12), which finally become disrupted, thus setting these trypomastigotes free, which again enter neighbouring cells (e.g. also in the heart) and are also destroyed. This constant destruction leads finally (mostly after years) to the death of humans. This mostly intracellular parasitism leads to the fact that immune reactions are low and thus infections with *T. cruzi* remain often undetected for years. In case bugs engorge such trypomastigotes during their blood meal, these stages become attached at their intestinal wall, develop into epimastigotes and introduce repeated binary fissions. In the terminal region of the intestine of the bugs again, stage transformation occurs and finally infectious trypomastigotes occur, which then are transmitted to humans or to other vertebrate hosts within a droplet of the bug's feces (Fig. 3.9). These infectious stages inside the hind gut of the vector bug are described as **metacyclic stages**.

4. **Symptoms of the disease (Chagas' disease, American trypanosomiasis)**: This disease is divided into an **acute** and a **chronic phase**. After introduction of the trypomastigotes (e.g. by skin scratching at the biting site of the bugs) into the body of a human or animal host, the parasitic stages become reproduced by repeated binary fissions in close nearness of the biting site. This increasing amount of parasites leads to a strong inflammation reaction, which is called **chagoma** and is often found close to the eyes. Typical symptoms are reddening and swelling of the cheek, the eyelids and conjunctiva (Romana sign). Also the preauricular lymph nodes may increase. After a 1–3 weeks long incubation period, the haematogenous distribution of the trypomastigotes is initiated. This phase is characterized by fever, lymph node swellings, hepatosplenomegalia and oedemas in the face and along the legs. Especially in children myocarditis

◄

Fig. 3.9 (continued) midgut of reduviid bugs (*Rhodnius* spp., *Triatoma* spp., etc.) after blood meal. These stages are attached to the intestinal wall and reproduce by binary divisions, thus being accumulated in high numbers. **6** Epimastigotes in the hindgut of bugs: they were transformed to metacyclic stages with a specific surface coat. **7** Metacyclic (=infectious) stage (trypomastigote) inside the rectum of bugs. These stages are set free in fecal droplets during blood meal on their hosts. They enter the skin after the blood meal through a bite channel, scratched skin or via mucous membranes. Inside the mammalian host they penetrate into various cells. *DS* developing surface coat; *F* flagellum; *HC* host cell; *KI* kinetoplast; *MI* mitochondrion; *N* nucleus; *NH* nucleus of the host cell; *SC* surface coat; *SF* short flagellum and meningoencephalitis may occur in an early phase of the disease and may lead to a quick death. However, in general most symptoms are reduced or even absent in the following months/years, although blood stages can still be diagnosed in Giemsa-stained blood smears (Fig. 3.10). These C- or S-shaped trypomastigotes, the kinetoplast of which is very large and situated at the pointed pole, are clearly distinguished from the related stages of the apathogenic species *T. rangeli*, which is also transmitted by bugs.

In the **chronic phase** of the Chagas' disease, which may run symptomless for many years (also called intermediate phase), parasitic stages appear rather seldom in the peripheral blood, since they reproduce themselves intracellularly inside host cells until lesions inside organs become obvious. Various types of host cells are damaged (Fig. 3.12) in addition to nerves leading to severe disturbances of the electrocardiogram. Cardiomyopathy often occurs, which is found mainly in the right ventricle. Acute and chronic inflammations in combination with fibrinozation often introduce cardiomegaly and neurisms inside the heart tip. The congestive cardiomyopathy leads finally within a few months to death. Lesions of the nerve system introduce arrhythmic transmissions of stimuli, which also can initiate sudden complete heart dysfunction. The destruction of nerve cells by parasites destroys nerve cells of many organs such as oesophagus, colon, kidneys, spleen, etc. and introduces formation of megaoesophagus, megacolon, etc. leading to dysphagia and obstipation. Such persons may die due to pneumonia and/or ileus obstipation.

5. **Diagnosis**: Trypomastigote stages (Fig. 3.10) most easily can be demonstrated during the **acute phase**. In fresh preparations they can be recognized by their movements. More details are seen in coloured smear preparations (Fig. 3.10), while the method of the so-called thick droplet has the advantage to show more stages, but the stages are mostly disrupted. Therefore other methods are needed to detect low infections of the peripheral blood system. Thus, e.g. the differential centrifugation and the use of the so-called micro-haematocrit method give better results, while the ion-exchange method according to Lanham is less effective in the diagnose of *T. cruzi* stages. Very effective is, however, the method described by Strout, which has to be carried out as follows:

- 10–20 ml blood is stored to let the blood cells sink at the bottom.
- Centrifugation of the overstanding serum is done for 5 min at 150 g and remnant erythrocytes are collected.
- Centrifugation of the remnant serum at 600 g concentrates the trypomastigote stages in the sediment, wherefrom they can be taken and microscopically diagnosed.

In the **acute phase** of *T. cruzi*, infectious trypomastigote stages can also be found in the fluid, from where they can be taken and microscopically diagnosed.

In the **chronic phase** of the Chagas' disease, direct diagnosis of *Trypanosoma* is mostly not possible. However, the so-called xenodiagnosis helps in about 50 % of human infections. Hereby 40–50 laboratory-reared (thus uninfected) bugs (e.g. *Triatoma* sp. as third- or fourth-stage nymphs) were enclosed each in a small vessel with a basic net. These containers were placed onto the arm of the tested person, thus giving the chance to get a blood meal by injecting the sucking mouthparts into the skin of the patient. After 30–60 days, the feces of these bugs are microscopically controlled for motile epimastigote stages (Fig. 3.11). Blood taken from potential hosts and cultured for weeks may also be helpful to detect blood stages (Fig. 3.12).

Serological investigations: Different types of serologic tests (e.g. IFT, ELISA, KBR, IHA, direct agglutination) show IgG antibodies in about 95 % of infected persons in the **chronic phase** of the infection, while during the **acute phase**, IgM antibodies were seen.

Negative results may be obtained during the first weeks after an infection, whereas **false positive results** can be obtained in the case of patients suffering from a leishmaniasis or from an infection with *Trypanosoma rangeli*.

PCR gives excellent results also during the chronic phase of the disease, but is, however, not available everywhere.

6. **Pathway of infection**: Infected bugs discharge during or after a blood sucking at human skin a droplet of feces containing infectious stages, which are rubbed into the biting site during scratching.
7. **Prophylaxis**: Bug control in houses with the help of insecticides.

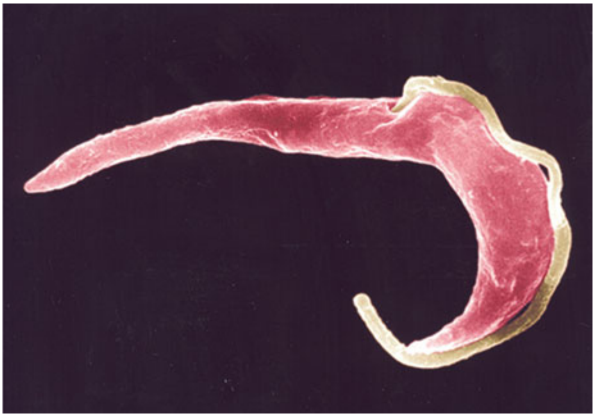

Fig. 3.11 Scanning electron micrograph of an epimastigote stage from the intestinal tract of the bug

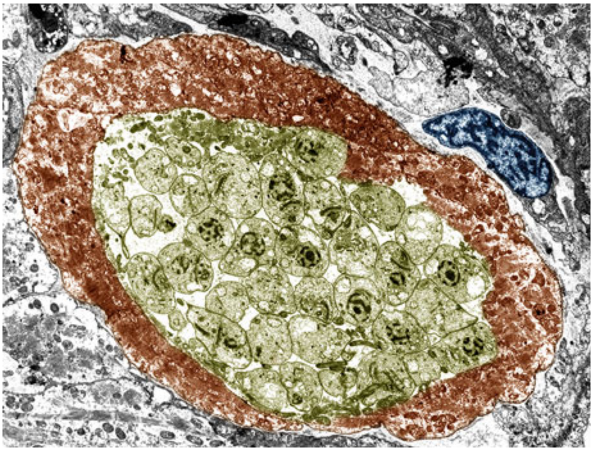

Fig. 3.12 Transmission electrin micrograph of a section through a muscle fiber (=pseudocyst) containing numerous epi- and trypomastigote stages

8. **Incubation period**: 50–20 days until occurrence of oedema (e.g. along the eyelid).
9. **Prepatency**: 1–2 months.
10. **Patency**: Eventually many years in cases of chronical courses.
11. **Therapy**: Very difficult; Nifurtimox (Lampit®) during the chronical phase: 8–10 mg/kg bodyweight is recommended for adults (in three divided doses) for 90 days; children should get higher doses (15–20 mg) for 90 days divided into four daily portions. Treatment should be done in the hospital. Benznidazole (Radanil®) is effective when given 5–7 mg/kg bodyweight in two divided portions for 60 days, while children should get daily 10 mg in the same way.

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3.6.2 *Trypanosoma rangeli*

1. **Name**: Greek – *trypanon* = drill; *soma* = body. The name of the species was given honouring the scientist Rangel from South America.
2. **Geographic distribution/epidemiology**: Guatemala, El Salvador, Costa Rica, Panama, Columbia, Venezuela and Brazil.
3. **Biology, morphology**: Trypomastigote stages are transmitted by the vector by its saliva while biting (**salivary infection**) to human hosts. The vectors are mostly kissing bugs of the genus *Rhodnius* (e.g. *R. prolixus*). Several species of mammals are reservoir hosts. The trypomastigote blood stages of *T. rangeli* reach 30 µm in length (*T. cruzi* stages measure only 20 µm), but their kinetoplast remains very tiny. They multiplicate in the blood fluid (not inside cells) by repeated longitudinal division. Intracellular stages do not occur and their number in the blood fluid is low. The multiplication of the parasite in the intestine of the vector bug leads to so-called epimastigote stages, which change their shape to trypomastigote forms, while moving to the saliva glands, from where they become transmitted to the next host.
4. **Symptoms of the disease**: Definitive, well-determined symptoms are mostly lacking.
5. **Diagnosis**: Xenodiagnosis is highly recommended because there are only few parasites present in the blood. About 2–13 weeks after the sucking of parasite-free

kissing bugs, stages of *T. rangeli* can be identified in the salivary glands of the vectors, if the host blood had been contaminated by parasites. Since the chemotherapy of *T. cruzi* infections may lead to severe side effects endangering health, mixing up of *T. cruzi* and *T. rangeli* should be strictly avoided. **Caution**: In case of the use of serological methods, cross-reactions with *T. cruzi* may occur.

6. **Pathway of infection**: Infections occur percutaneously with saliva injection of the vector while sucking human blood (**salivary infection**).
7. **Prophylaxis**: Control of kissing bugs in houses using sprays containing insecticides, especially at possible hiding places (behind ledges, in wall gaps, etc.).
8. **Incubation period**: The infection occurs mostly unnoticed, because *T. rangeli* is apathogenic.
9. **Prepatent period**: 1 week.
10. **Patency**: Years.
11. **Therapy**: Not necessary.

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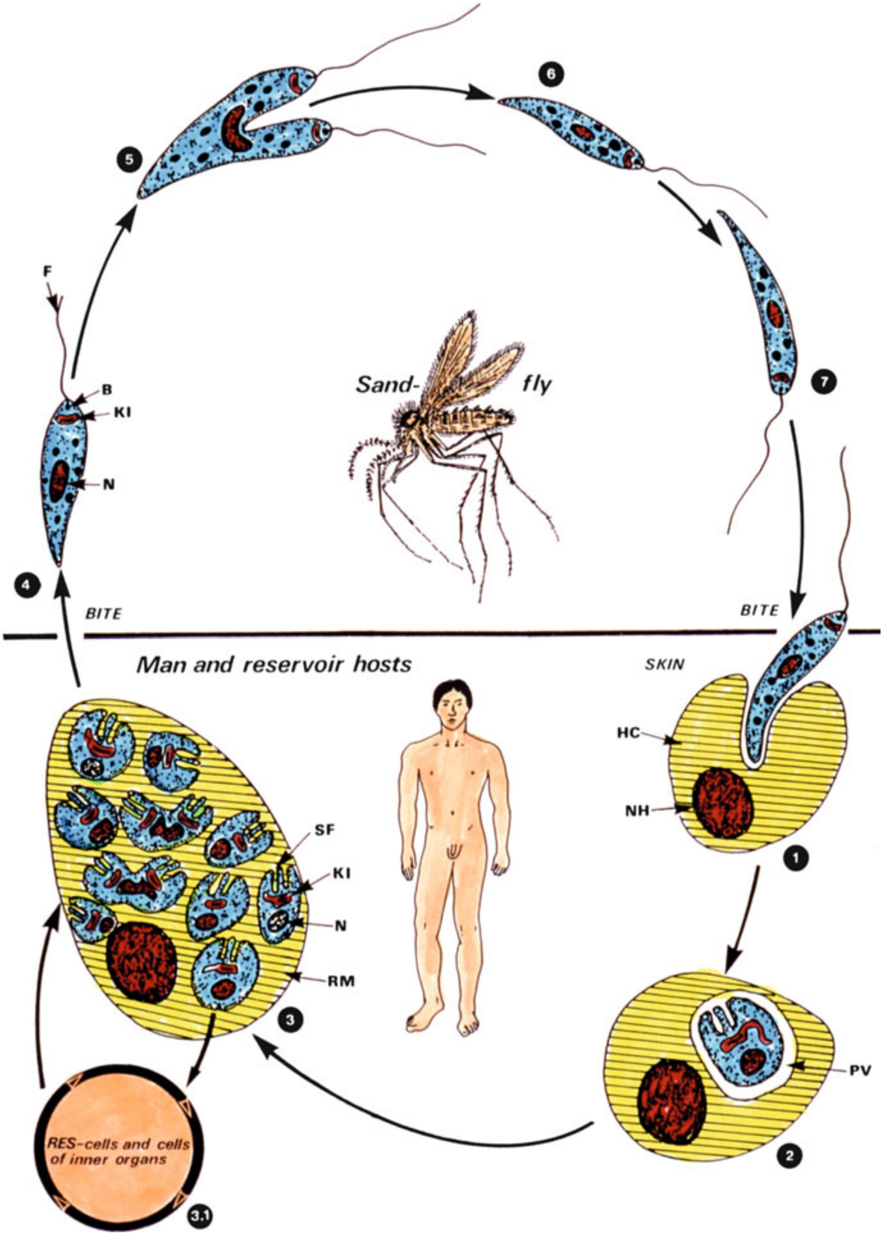
3.7 *Leishmania* species (Agents of the Skin, Mucosa and American Leishmaniasis)

1. **Name**: The name of the genus honours the English scientist W.B. Leishman (1865–1926).
2. **Geographic distribution/epidemiology**: Dry, sandy rocky regions; *L. donovani infantum* (countries around the Mediterranean Sea), *L. tropica* (Southern Balkan, Greece, Turkey, Caucasian countries, Saudi-Arabic Coastline, Afghanistan, Pakistan), *L. major* (Northern Africa, Middle East and Lebanon, Iraq, Syria, Northern Saudi Arabia, Iran, Southern Afghanistan, Pakistan, regions around the Black Sea, in Western Africa between 10th and 13th meridian, focally in Middle and Central Africa), *L. aethiopica* (Ethiopia, Kenya, Tanzania, Namibia), *L. mexicana* complex (Texas, Mexico to Northern Argentina and to Peru in the West of South America), *L. braziliensis* complex (Eastern Middle America) and the same *L. mexicana*. More than 100 million people are infected (Table 3.1).
3. **Biology, morphology**: The bite of the during dusk active female sandflies (genera *Phlebotomus*, *Lutzomyia* or *Sergentomyia* (Figs. 5.61, 5.62) starts the infection. In these cases so-called promastigote stages (their flagellum protrudes at the apical pole) are transmitted (Figs. 3.13, 3.15, 3.16). Inside the skin they enter cells of the endothelium, histiocytes and macrophages. There they are transformed to very tiny amastigotes (2–4 µm) containing a

Table 3.1 Disease manifestations and transmission of some predominant *Leishmania* species found in the New and Old Worlds (according to Pace 2014)

Leishmania (L) species	Sandfly vector (*Phlebotomus* [P] or *Lutzomyia* [L] species	Main affected areas	Reservoir hosts	Disease manifestations
L. aethiopica	*P. longipes* *P. pedifer*	Ethiopia, Kenya	Hyraxes	Cutaneous, diffuse, mucosal
L. amazonensis	*L. flaviscutellata*	East Andes	Rodents	Cutaneous, disseminated
L. braziliensis	*L. ovallesi* *L. wellcomi* *L. neivai* *L. whitmani*	East and West Andes	Rodents, marsupials, dogs	Cutaneous, mucosal
L. donovani	*P. argentipes* *P. martini* *P. orientalis*	India, Bangladesh, Nepal, Bhutan, Sudan, Ethiopia	Humans	Visceral
L. guyanensis	*L.umbratilis*	East Andes	Arboreal edentate mammals	Cutaneous, mucosal
L. infantum (same as *L. chagasi* in the New World)	*P. ariasi* *P. perniciosus* *L. longipalpis*	Mediterranean region Latin America	Dogs	Visceral, cutaneus
L. major	*P. dubosqi* *P. papatasi*	Sub-Saharan Africa North African, Middle East, Iran, Pakistan, India	Rodents Gerbils, rodents	Cutaneous
L. mexicana	*L. olmeca olmeca*	West Andes	Rodents, marsupials	Cutaneous, diffuse, mucosal
L. panamensis	None proven	West Andes	Arboreal edentate mammals	Cutaneous, mucosal
L. peruviana	None proven	Peru	Rodents, marsupials, dogs	Cutaneous, mucosal
L. tropica	*P. sergenti* *P. arabicus*	North Africa, Middle East, Iran, Afghanistan North and Sub-Saharan Africa	Humans Hyraxes	Cutaneous



5
6
F
B
KI
N
7
Sand-
fly
4
BITE
BITE
Man and reservoir hosts
SKIN
HC
NH
1
SF
KI
N
RM
3
PV
2
RES-cells and cells of inner organs
3.1

Fig. 3.13 Life cycle of ***Leishmania* species**. (**1**) A promastigote stage is taken up by a macrophage in human skin right after the bite of the sandfly (mostly with the flagellum in the front). (**2**) Transformation to a micromastigote stage (in the cytoplasm of the host cell, in vacuoles – so-called phagosomes) within 24 h. (**3**) Reproduction by repeated binary fission inside the host cell cytoplasm after parasitophorous vacuoles have been disrupted. Finally the host cells will be severely stretched and lately burst. Then the parasites lying in the remnants of the cytoplasm of the host are set free. (**3.1**) Species of the *L. donovani* complex infect the cells of the RES of inner organs with their

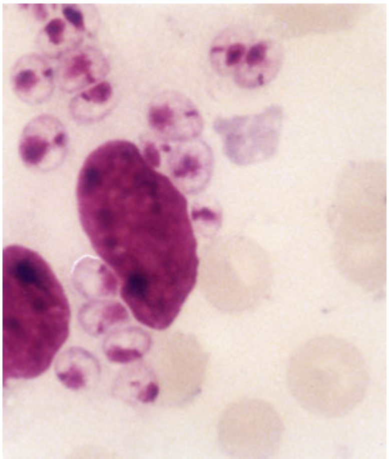


Fig. 3.14 Light micrograph of a smear preparation with amastigote stages of *L. major* besides a bursted host cell and the nucleus

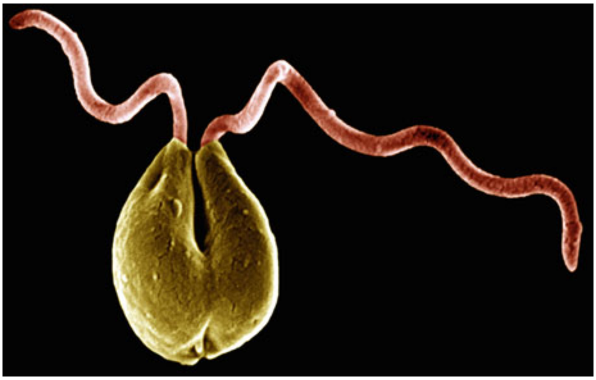


Fig. 3.15 Scanning electron micrograph of a promastigote stage of *Leishmania* sp. during binary fission

central nucleus and a kinetoplast with typical strands of DNA. Their flagellum cannot be observed by light microscopy, because it is too short and does not protrude the cell surface (Fig. 3.14). Host cells in the area around the bite site are mostly damaged due to the repeated divisions of the parasite. Therefore these zoonotic pathogens will spread concentrically around the bite sites. The

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Fig. 3.13 (continued) micromastigote stages. (**4**) Micromastigote forms are taken up by the sandfly during the bite. They are transformed into promastigote stages in the upper intestine of the vector, being attached at the intestinal mucosa with their flagellum. (**5**) Reproduction by longitudinal division. (**6**, **7**) Final differentiation into the infectious stages. The peritrophic membrane of the vector has the shape of a sack; the parasites develop themselves into infectious stages and multiply repeatedly. Finally they enter the anterior portion of the intestine and thus reach a new host during blood meal of the sandfly. These infectious stages are so-called metacyclic stages (4–8 µm in length). The total development with different transformations in the sandfly takes only about 5 days. All infectious stages show a thin surface coat, which is different in the cases of the two hosts (sandfly, humans). *B* basal apparatus; *F* flagellum; *HC* host cell; *KI* kinetoplast; *N* nucleus; *NH* nucleus of the host cell; *PV* parasitophorous vacuole; *RES* reticular endothelial system; *RW* relicts of the host's cytoplasm; *SF* short flagellum; *WZ* host cell

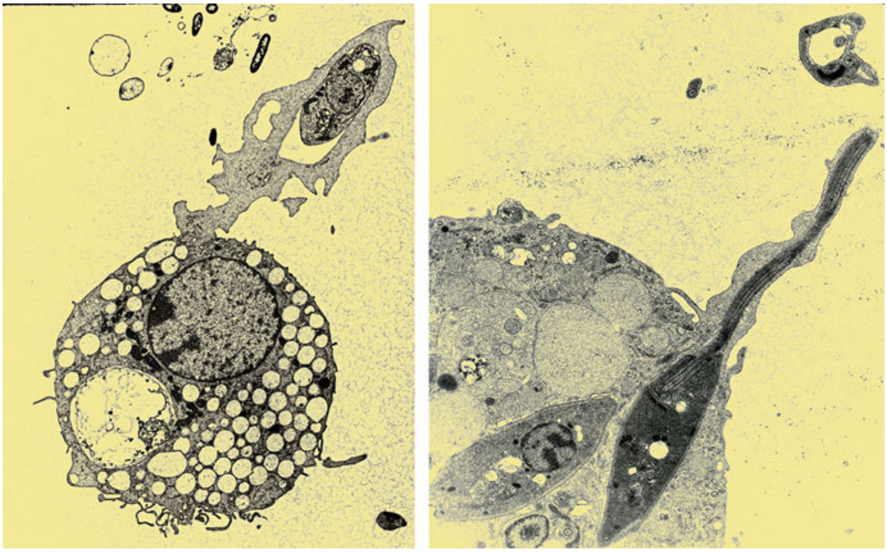

Fig. 3.16 Transmission electron micrographs of sections through macrophages ingesting promastigotes of *Leishmania* sp.

stages of the **salivary leishmaniasis** are only rarely found in the blood or inside local lymph nodes. Thus spreading of these parasites can be seen only locally around the area of the bite site. Therefore these parasites can most easily be demonstrated with the help of biopsies and smear preparations taken from borders of infected skins. When the sandfly bites again, it ingests further amastigotes, which then are transformed to large amounts of infectious promastigotes in the intestine of this fly; the life cycle is closed (Fig. 3.15, 3.16). All these species have reservoir hosts (*L. tropica* – dogs, rodents; *L. aethiopica* – cape hyrax, rock hyrax; *L. mexicana* complex – rodents). They all are reserve hosts from where the parasites can be transmitted again to humans via bites of sandflies. After overcoming a previous infection successfully, the host is immune to a new infection by the same *Leishmania* species. The spread of these pathogens among the reservoir hosts is very common so that the skin leishmaniasis can be categorized as a typical zoonosis.

4. **Symptoms of the disease**: "Skin leishmaniasis" is a collective name for several clinically different appearances of symptoms which can be initiated by only one or some different zoonotic pathogens of the genus *Leishmania* (Fig. 3.17, Table 3.2).
   (a) **Old World – skin leishmaniasis**
      - **Dry skin leishmaniasis** (*L. tropica*, *L. infantum*)
      - **Humid skin leishmaniasis** (*L. major*, Oriental and Aleppo sore
      - **Diffuse skin-/mucosa leishmaniasis** (*L. aethiopica*)

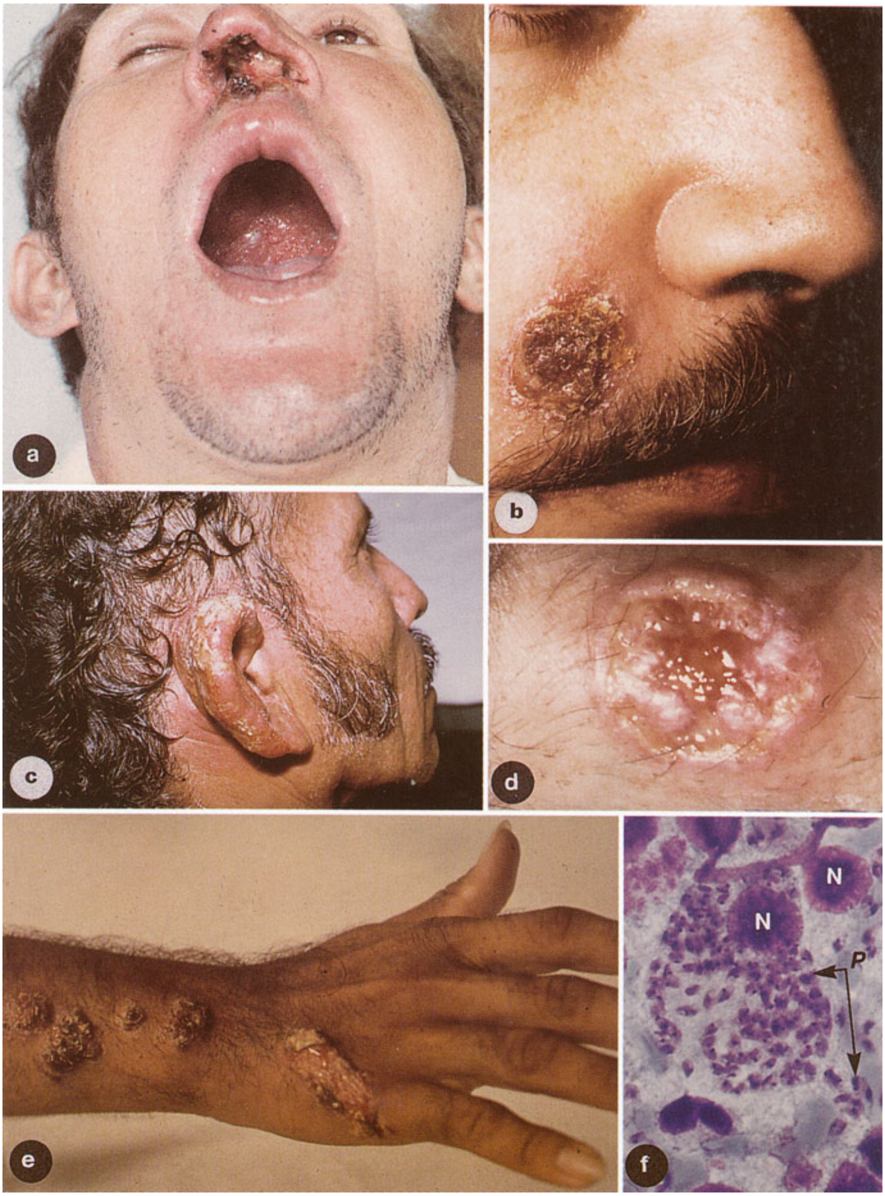

Fig. 3.17 Different aspects of symptoms of leishmaniasis (**a**–**e**) and *Leishmania* stages (**f**). (**a**) Symptoms of leishmaniasis of the mucosa (**espundia**) in the nose and throat of a Columbian forest worker; (**b**) symptoms of **espundia** close to the lips of a South American; (**c**) **Chiclero's ulcer** at the ear, caused by *Leishmania mexicana* shown at a Mexican; (**d**) skin leishmaniasis at the arm caused by *L. tropica* (**oriental sore**); (**f**) Giemsa-stained smear preparation of the skin near an ulcer; numerous parasite stages (P) have multiplied in a macrophage, now bursted (*N* nucleus)

Table 3.2 Clinical presentation of cutaneous leishmaniasis caused by Old World species (Pace 2014)

Old World species	Clinical features
L. infantum	Single nodules May ulcerate May resolve spontaneously within 1 year but leave atrophic scars
L. tropica	Multiple painless dry ulcers Heal spontaneously over 1 year but tend to leave disfiguring scars
L. major	Severely inflamed multiple ulcers, may coalesce Heal slowly, leave disfiguring and disabling scars
L. aethiopica	Localized nodules; oronasal lesions causing localized anatomical distortion Heal over 2–5 years Causes disseminated cutaneous leishmaniasis more frequently on limbs and face No ulceration unless immunosuppressed

(b) **New World – skin leishmaniasis**
- **Chiclero ulcer** at the ear (*L. mexicana mexicana*)
- **Espundia**, leishmaniasis of the mucous membranes (*L. braziliensis braziliensis*)
- **Diffuse skin leishmaniasis** (*L. mexicana amazonensis*, *L. mexicana pifanoi*)
- **Uta dry skin leishmaniasis** (*L. braziliensis peruviana*) (Table 3.3)

In general: Intense itchy pruritic papules and nodules of reddish colour occur after an incubation time of 2–4 weeks (seldom after several months) at the injection site. They ulcerate slowly.

The different clinical appearances vary not only dependent on the species of the parasite but also on the grade of the immunologic reaction of the individual host organism. In the case of an infection with *L. tropica* (**Old World oriental sore**), spontaneous healing occurs after several months (usually 1 year); however, bacterial superinfections may complicate the healing process, leaving a hyperpigmented flat scar.

In the case of the **South American leishmaniasis** infections, there are two main cure differences between the main species: *L. mexicana* leads to a cutaneous leishmaniasis with a tendency to spontaneous healing, as it occurs in the case of the orient sore. The consequences of an infection with *L. braziliensis* are more severe. In this case a lymph- or blood stream-transmitted distribution leads to a spread to other regions of the skin appearing as **espundia**. This infection of the nose may destroy the mucosa of the nose and mouth, infiltrate the lips, change the lymph stream and destroy the nasal cartilage leading to the symptom of a so-called tapir nose. Without treatment dozens of further ulcus or hyperkeratotic lesions on the face, neck, shoulders

Table 3.3 Clinical presentation of American cutaneous leishmaniasis

Disease pattern	New World species	Clinical features
Localized cutaneous leishmaniasis (LCL)	*L. mexicana* *L. braziliensis* *L. panamensis* *L. guyanensis* *L. peruviana* *L.infantum (chagasii)*	– Single/multiple nodules or ulcers – May be associated with lymphadenopathy/ lymphadenitis – May spread to other areas of skin or mucosa (see MCL) – Appearance of *L. infantum* lesions similar to Old World lesions (same species)
Mucocutaneous leishmaniasis (MCL)	*L. braziliensis* *L. panamensis*	– Lymphatic/haematogenous metastasis to mucosa of mouth and upper respiratory tract – Risk increased with delayed healing of primary skin lesion – May appear months to years after healing of cutaneous lesion – Seen with other species in immunocompromised
Diffuse cutaneous leishmaniasis (DCL)	*L. mexicana* *L. braziliensis* *L. panamensis* *L. amazonensis* *L. guyanensis*	– Multiple cutaneous nodules or ulcers (>20 to hundreds)_mucosal involvement – May be resistant to antimonial treatment – Distinct disseminated and borderline disseminated cutaneous forms also described in Brazil: single/multiple chronic relapsing lesions

and arms may follow. Recent reports indicate that some species of the skin-leishmaniasis parasites can also lead to the symptoms of visceral leishmaniasis.

5. **Diagnosis**: In the case of cutaneous or mucocutaneous leishmaniasis, the parasites can be detected in probes or smear preparations taken from the lesions of skin or mucosa. Material of fresh lesions especially at the edge areas is used for tipping preparations to become coloured by Giemsa stain. Further material is needed for tissue culture. The typical structure of the *Leishmania* parasites can best be seen in a preparation with the help of the immune-peroxidase method. Examination of histological sections is not recommended. Numerous parasites are present in the case of the **cutaneous leishmaniasis** of the **Old World** (*L. tropica, L. major*) and especially in the case of the diffuse cutaneous leishmaniasis, where the pathogens can easily be detected. Unfortunately the **cutaneous** and **mucocutaneous leishmaniasis** of the **New World** show only low numbers of parasites. Thus the direct proof is here mostly difficult as well as in the cases of recidives of a leishmaniasis and those of the post-kala-azar leishmanoid. Parasitic stages of the *L. braziliensis* group are difficult to isolate and cultivate. Thus it is here recommended to start tests by inoculation of probes in the paw or in the nose of golden hamsters.

   Serology (IFT, ELISA a.o. tests) is mostly positive in the case of mucocutaneous infections. Antibodies cannot be identified or only in low concentrations. Recidives and diffuse cutaneous leishmaniasis are mostly seronegative. An exact differentiation of the species and subspecies is possible by means of electrophoretic isoenzyme analysis of monoclonal antibodies and DNA in situ hybridization. The PCR is today a very common technique as it is a very sensitive method to detect and to differentiate species from each other.

6. **Pathway of infection**: Percutaneous transmission during bites of sandflies (Figs. 5.61, 5.62).
7. **Prophylaxis**: Application of repellents (e.g. Viticks®) on skin and clothes helps to protect against bites of the vectors. A vaccination with living pathogens was tested in endemic regions in order to establish an immunity; however, the success remained low.
8. **Incubation period**: 2–4 weeks, in rare cases up to 1 year.
9. **Prepatent period**: 1–3 weeks.
10. **Patency**: Many months
11. **Therapy**: A systemic therapy is not justified in cases of simple cutaneous leishmaniasis because of the tendency of self-healing and the potential toxicity of the drugs. If necessary, only repeated perilesional injections with 1–3 ml (100–300 mg) sodium stibogluconate as well as treatment of secondary bacterial infections should be done. A systematic therapy, however, is strongly recommended in cases of mucocutaneous leishmaniasis; diffuse cutaneous, disseminated or deforming cutaneous leishmaniasis; and visceral leishmaniasis (Table 3.4).

Table 3.4 Drugs used to treat the various forms of leishmaniasis (Pace 2014)

Drug	Mode of action on the parasite	Route and main indication
Pentavalent antimonials – Sodium stibogluconate – Meglumine antimon	Inhibition of glycolysis and fatty acid oxidation Dose dependent inhibition of ATP and GTP formation	im/iv: VL, CL, MCL, PKDL intralesional: CL
Pentamidine isethionate	Inhibition of polyamine biosynthesis and disruption of mitochondrial membrane potential	im: CL, MCL Intralesional: CL
Amphotericin B and lipid formulations	Inhibition of cell membrane synthesis by binding to ergosterol Pore formation in cell membrane	iv: VL, CL, MCL, PKDL
Paromomycin	Possible interference with RNA synthesis and membrane permeability	im: VL Topical: CL
Allopurinol	Interference with protein synthesis (purine salvage cycle)	Oral: VL, CL

VL visceral leishmaniasis; *CL* cutaneous leishmaniasis; *MCL* mucocutaneous leishmaniasis; *PKDL* post-kala-azar dermal leishmaniasis; *im* intramuscular; *iv* intravenous

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3.8 *Leishmania donovani* complex (Visceral Leishmaniasis)

1. **Name**: The origin honours the two English discoverers of the species = W.B. Leishman (1865–1926) and Charles Donovan (1863–1951).
2. **Geographic distribution/epidemiology**: Dry, sandy mountain regions:

   Leishmania donovani donovani: India, China, Central Asia, Eastern Africa reaching from Egypt to Kenya and Uganda, Western Africa with Senegal, Mali, Nigeria.

   Leishmania donovani infantum: Baleares, Corsica, Sardinia, coasts of the Mediterranean Sea and Black Sea area, Middle East with Saudi Arabia, Yemen, Iraq, Iran, Ethiopia and China.

   Leishmania donovani chagasi: Central and South America, focally from Mexico to Southern Brazil and North of Argentina. More than 100 million people are infected.

3. **Biology, morphology**: It is not yet clear whether the *L. donovani* complex comprises three subspecies or three independent species, especially since they cannot be distinguished morphologically. The infection of humans is induced by the bite of female sandflies belonging to the genus *Phlebotomus* (*L.d. donovani*, *L.d. infantum*) or *Lutzomyia* sp. in case of *L.d. chagasi* (Fig. 5.61).

   The so-called promastigote stages (10–20 µm in length and provided with a front flagellum) are regurgitated into the bite site together with intestinal contents during feeding. These promastigotes are ingested by macrophages in the skin of the host and enclosed into food vacuoles inside the macrophage. There they transform themselves to avoid amastigote or micromastigote stages (2–4 μm in length). The flagellum is situated in a deep flagella pocket and never protrudes from the surface. Therefore this short flagellum is only visible in electron micrographs, while Giemsa-stained blood smears do not show it. The parasite inside the digestion vacuole divides permanently, and up to 20 amastigote stages may be formed until finally the macrophage bursts and releases the parasites which immediately attack and invade neighbouring cells. Repeated multiple reproduction in cutaneous areas can lead to large skin lesions also in the case of the species of the *L. donovani* complex.

However, the zoonotic pathogens soon disappear from the cutaneous areas and invade the RES (reticuloendothelial system) of the intestine, liver, spleen, bone marrow and lymph nodes of humans.

As soon as the sandfly has taken up such amastigotes, they transform themselves into promastigotes in the anterior intestine and multiply themselves by longitudinal divisions. Then they can become regurgitated during the next sucking act of the vectors.

All three cited pathogens infect not only humans but also several animal species, which act as so-called reservoir hosts. In the case of *L.d. infantum*, mostly dogs, wolves, foxes, racoons and rats are involved. In the case of *L.d. chagasi*, only foxes and dogs are very important reservoir hosts. After having overcome an infection, humans are very rarely hit a second time due to a strong acquired immunity.

4. **Symptoms of the disease (Kala-Azar, dum-dum fever, black disease, visceral or intestinal leishmaniasis)**: Most of the infections are not noted. However, in the case of malnutrition or immunosuppression (e.g. in case of HIV infections, AIDS-syndrome), the infection can become manifested.

   In the case of an infection, the incubation period can vary from a few weeks to several months. Fever generally occurs (however, without shivers) reaching up to 39 and 40 °C and lasting for several weeks. These fevers may be interrupted by a fever-free phase and finally end in a low-grade fever continuum. In the phase of high fever temperatures, in general two fever peaks occur within 24 h. In addition to fever, the main symptom of the disease is a growing splenomegaly, but sometimes hepatomegaly and lymph node swellings occur, too. Further an increasing anaemia and leukopenia (numbers of leucocytes range below 2000/mm^3 in 75 % of the cases) occur. Also the number of the thrombocytes is heavily reduced. However, eosinophilia never occurs! Gammaglobulines are strongly increased, but albumin appears low grade in electrophoresis. The erythrocyte sedimentation reaction is very fast due to the anaemia and the change of protein compounds. The colour of the skin can turn from pale to ashen-faced. The visceral leishmaniasis leads to death without treatment. Death occurs in this case starting after 6 months up to 3 years during a phase of cachexia mainly induced by bacterial complications. Differential diagnosis at the starting point of the infection must consider the following other diseases with splenomegaly: malaria, typhus, (miliar-) tuberculosis, sepsis, brucellosis, schistosomiasis in the late phase or hepatosplenomegaly, lymphomas and leukaemia.

If a visceral leishmaniasis has been treated successfully, after 1–10 years, the symptoms of the dermal post-kala-azar leishmaniasis (DPKL) may occur as a long-term complication. In this case heavily pigmented or erythematous nodes of the skin appear, mostly in the face (20 % of the cases in India, 2 % of the cases in Africa).

5. **Diagnosis**: In the case of **visceral leishmaniasis**, the amastigotes of *L. donovani* can be diagnosed in punctates of the spleen, bone marrow, lymph nodes, liver as well as in the blood stream (listed here in a descending grade of sensitivity).

   Punction of the spleen is, however, risky because of thrombopenia which is often occurring (additionally in the case of reduced number of coagulation factors). That is why mostly other diagnostic methods are preferred: punctates or carefully prepared biopsies of the bone marrow, which can be examined with the help of Giemsa-stained or by panoptically dyed probes (Pappenheim). Additionally culturing (NNN-Agar, Schneider's *Drosophila*-medium a.s.o.) is recommended. Isolation of the parasites in experimentally infected gold hamsters is also possible after i. p. inoculations. Positive results by means of tipping preparations of the spleen, however, can be seen only after 6–8 weeks. Detection of the parasites in peripheral blood is mostly impossible due to the generally low amount of parasites occurring therein. PCR methods to detect the DNA of *Leishmania* stages taken from the bone marrow are still at the experimental stage. Serodiagnosis (IFT, ELISA and other methods) can successfully be used since they show mostly high titres of antibodies. However, cross-reactions may often occur in the cases of cutaneous and mucocutaneous leishmaniasis, as well as in the case of the Chagas' disease. False negative results are possible in the final stage of the disease and in the case of immunosuppressed persons.
6. **Pathway of infection**: Percutaneous during blood-sucking bites of sandflies.
7. **Prophylaxis**: Applying of caridin-containing repellents (e.g. Autan®, Viticks®) on the skin and on clothes in high-risk areas; sleeping under a bed net.
8. **Incubation period**: 10–60 days, in some cases up to 1 year.
9. **Prepatency**: 1–3 weeks.
10. **Patency**: Months to years. Self-healing cases are very rare. Without treatment lethal outcome is common.
11. **Therapy**: The method of choice in the case of visceral leishmaniasis is the application of grade 5 antimony (Sb) medication: natrium stibogluconate and meglumine antimonate at a concentration of 20 mg Sb/kg body weight daily im or iv over a period of 30 days. The healing rate is, however, mostly not higher than 90–95 %. In the case of resistance against antimony or in case the product is incompatible, there are some other successful medicinal devices: pentamidine and amphotericin B as well as paromomycin (im) or allopurinol,

respectively, the combination of antimony with gamma-interferon medicaments. Miltefosine (Impavido®) is a drug which can be taken orally (three doses covering in total 1.5–2.5 mg/kg bodyweight daily for a period of 28 days).

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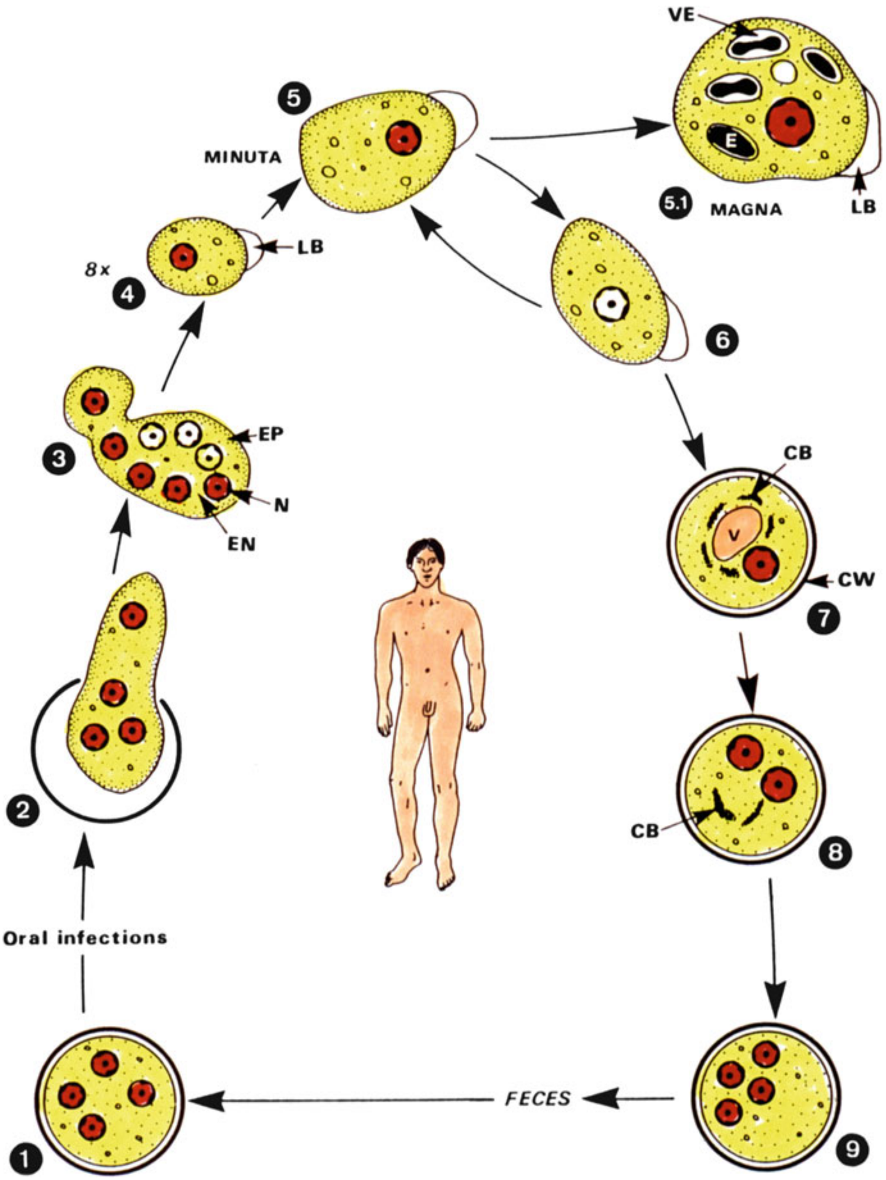
3.9 *Entamoeba histolytica* (Entamobiasis, Amoebiasis and Bloody Flu)

1. **Name**: Greek – *entos* = inner, *amoibos* = shape, changing, *histos* = tissues, *lysis* = dissolution. Engl: *amoebic diarrhoea*.
2. **Geographical distribution/epidemiology**: Countries with high temperatures; however, agents of disease may be introduced also in temperate countries; more than 500 million people are infected worldwide; 75,000–100,000 of them die per year.
3. **Biology, morphology**: This potentially rather aggressive amoeba occurs in three stages inside the intestine of humans (Figs. 3.18, 3.19):
   (a) Minuta form (10–20 μm)
   (b) Magna form (20–35 μm)
   (c) Cysts (10–15 μm)

   Motile minuta and magna stages are characterized by single hyaline, suddenly protruding pseudopodia. The dense endoplasm contains food vacuoles, which in the case of magna stages also include erythrocytes. Besides these food vacuoles, the central endoplasm also surrounds the globular nucleus, which is characterized by a central nucleolus (Fig. 3.19a). In stained preparations and in cysts, the nucleus appears ring-shaped with a dense dot = nucleolus (Fig. 3.19c). Inside intestinal fluid the minuta stages are reproduced by a binary


VE
5
MINUTA
E
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MAGNA
LB
8x
4
LB
6
3
EP
N
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CB
V
CW
7
2
CB
8
Oral infections
FECES
1
9

Fig. 3.18 Diagrammatic representation of the life cycle of *Entamoeba histolytica*, which starts when humans ingest four nuclei-containing cysts in contaminated food. *CB* crystalline body; *CW* cyst wall; *E* erythrocyte; *EN* endoplasm; *LB* lobopodium; *N* nucleus; *V* vacuole; *VE* digestion of erythrocytes in an inner food vacuole

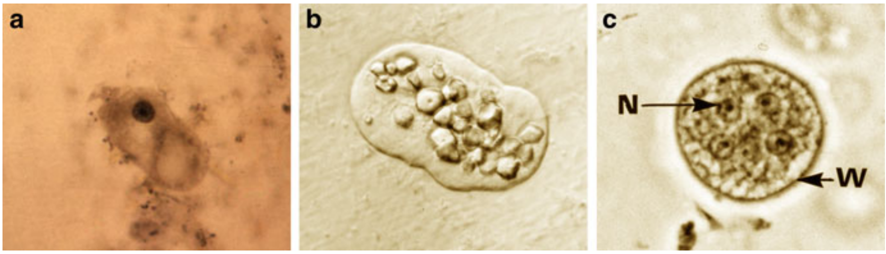

Fig. 3.19 *Entamoeba histolytica*: light micrographs of a minuta stage (**a**), of a magna stage (**b**) and of a cyst (**c**); *N* nucleus; *W* cyst wall

fission process, which may lead to two often differently sized daughter cells, which quickly grow up by the formation of food vacuoles. Even millions of such stages may occur in persons living in endemic tropical regions without introducing symptoms of disease. Some of these minuta forms grow into so-called magna forms (Fig. 3.19b), which attach to the surface of the intestinal cells of the host, especially in the posterior region of the intestine, with the help of peculiar structures (amoebapore) inside their limiting membrane to destroy these intestinal cells and thus enter the intestinal wall and the blood vessels. Inside the intestinal wall, these magna forms ingest via formation of food vacuole portions of destroyed host cells and red blood cells (Fig. 3.19b). The blood stream transports such magna forms throughout the whole human body. Especially in the liver but also in the lung wings and (even more seldom) in the brain, so-called abscesses (Fig. 3.21) are formed by massive destruction of host cells. These abscesses may reach diameters of 15–20 cm in the liver and are filled by a fluid containing destructed host cells and erythrocytes. Such abscesses may lead to death.

The "normal development" of the intestinal minuta forms finds its end (after numerous divisions) in the colon and rectum by encystation and formation of a tiny-walled cyst (Fig. 3.19c). Inside this cyst the nucleus divides and finally 4-nuclei are present, when the cysts are excreted within the feces of the infected person. Infected persons may excrete – even without severe symptoms of disease – up to 30 million cysts per day. However, since the cysts in most of such enormous excretions are not studied by molecular biological techniques, it might be that these large numbers are not produced by *Entamoeba histolytica* but by *E. dispar*, which looks nearly identically but is practically nonpathogenic. Serial fecal investigations of the group of Tannich (Hamburg) showed that more than 90 % of mass excretions of cysts are due to *E. dispar*, which, however, does not produce magna forms.

4. **Symptoms of the disease (Entamoebiasis, amoebic red flu)**: After a short phase (of a few days) or after a longer-lasting symptomless reproduction of the minuta stages, an invasion of the intestinal wall may occur due to penetrating

magna stages. Therefore it is merely impossible to define a correct incubation period. During the ongoing infection, the following can be determined:

(a) **Intestinal amoebiasis**

After infection mostly only slight gastrointestinal symptoms occur (such as abdominal pain, nausea without vomiting, feeling of an intestinal pressure, but no fever). In contrast to these rather slight symptoms, bacterial enteritis starts heavily with fever and strong phases of diarrhoea. The feces of *Entamoeba*-infected persons are mostly well formed or somewhat smooth and slimy. During the following days, the numbers of defecations increase up to 5–10 per day (in the case of bacterial enteritis, there are even more!). Only in rare cases completely watery feces are excreted. In cases of intestinal wall invasions, such stools may contain traces of blood (Fig. 3.20). These bloody aspects are in strict contrast to the watery, non-bloody feces due to bacterial infections. In these cases the excreted feces appear whitish and yellowish. In a later phase of entamoebiasis, the colon surface becomes severely damaged and different types of ulcus formations occur. In case these regions become superinfected by bacteria colics, severe abdominal pain, weakness and relapsing fevers increase considerably. In increasing numbers blood vessels are destroyed so feces appear permanently reddish. In a considerable number of infected persons, symptoms of a colitis ulcerosa occur as well as complications such as so-called amoebomas. This term describes a local, protruding inflamed benign tumour, which blocks the fecal passage. As follow-up of different secondary bacterial infections, perforations of the intestine may occur. In cases of a following **peritonitis**, the infection may lead to death. Disappearance of slight to medium symptoms of an entamoebiasis does not exclude a persistent infection.

(b) **Extraintestinal amoebiasis**

Although in many cases the symptoms of amoebiasis may be reduced after a while, this does not exclude the fact that abscesses may form inside the liver, lungs or even brain (Fig. 3.21). This process may start months

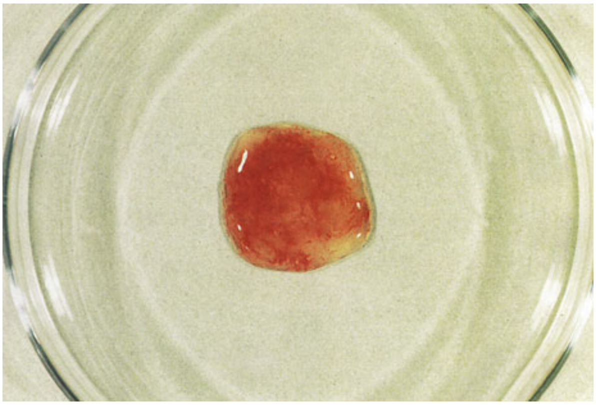

Fig. 3.20 Probe of a portion of bloody diarrhoeal feces

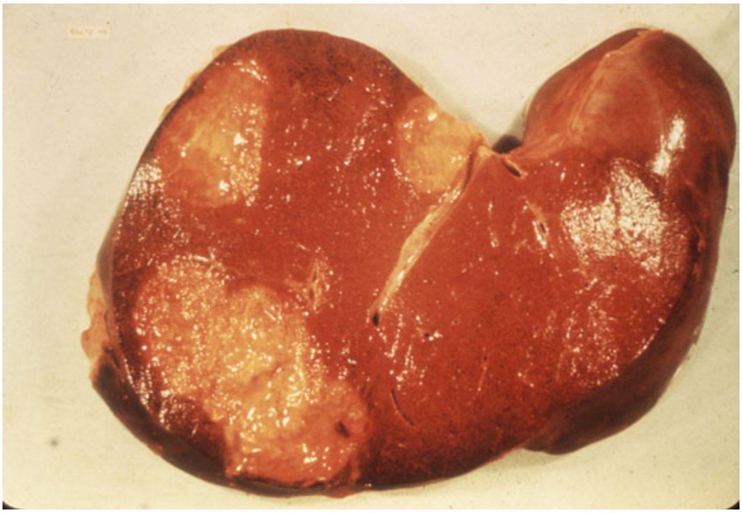

Fig. 3.21 Section through a human liver showing several, yellowish abscesses

after the oral infection by ingesting cysts within contaminated food or drinking water. There are also cases described where this peculiar organ infection only occurred many months or even years after the infection. In cases of liver abscess, there are no true abscesses bordered by a limiting membrane but only hollows in the damaged liver due to blood vessel disruption; first symptoms include weakness, low fever (38–39 °C) without shivers and general bad feeling and diffuse abdominal pain. Most of the liver abscesses are developed inside the right portion, grow quickly to a large size and introduce dull pressure pain. Patients lay mostly left-bended in their beds, breath only surfacely and refuse touching of the belly. Occasionally an inflamed infiltration fluid is developed at the right lateral thorax wall. This event in combination with a high-grade leucocytosis (often more than 20,000 μl) and an enormous blood sedimentation indicates significantly an amoebic abscess, which can be diagnosed finally with the help of computer tomography. In such cases chemotherapy should be started immediately, which reduces very quickly pain, liver swelling, fever and the humoral fever parameters. If such a quick effect is not seen, other reasons such as a liver tumour, echinococcosis and bacterial abscesses must be considered, too. It was noted that in cases of delayed chemotherapy, complications occur such as the perforation of the abscess, followed by deloading of the abscess fluid into the body cavity or (depending on the site of the abscess) also into pleural cavity. All these complications need urgent chirurgical activities.

5. **Diagnosis**: In the case of the **intestinal entamoebiasis**, the small-sized **trophozoites** (minuta stages) can be diagnosed in endoscopically obtained material. These trophozoites show the typical single, quickly protruding a hernia-sac-like pseudopodium (Fig. 3.19a). The large (20–40 μm) tissue invading magna stages (Fig. 3.19b) can be easily diagnosed, since they contain very often erythrocytes. In the cases that an immediate investigation of the intestinal fluid is not possible, a preservation of the diagnostic material can be done by storage in different solutions such as MIF, SAF or PVA. In coloured smear preparations (e.g. using Heidenhain, Trichrome or Lawless solutions) which can be done with fresh or fixed material, the trophozoites of the invasive *Entamoeba histolytica* can be significantly differentiated from noninvasive species (such as *E. coli*, *E. dispar*, *E. hartmanni* – see Chap. 10.3). Tissue-invasive stages can be diagnosed in biopsies obtained from the colon wall.

   The cysts of *E. histolytica* are most easily demonstrated with the help of microscopical investigations of the sediment of probes obtained after the use of MIF or SAF concentration methods.

   Culture methods (e.g. in Robinson medium) can be used additionally in cases where symptoms of an entamoebiasis are seen, but cyst stages are not found.

   A species determination of the different *Entamoeba* species based only on morphological criteria is not possible. Especially the differentiation between pathogenic and nonpathogenic species (strains) needs special methods (DNA in situ hybridization, PCR, etc.).

   Serodiagnostic methods (ELISA, IFT) help only in cases of an invasive amoebiasis, but initial infections may remain undetected, so that repeated tests have to be done.

   Liver abscess detection may be done with the help of computer tomograms (CT) or sonograms but will only be successful with an incubation period of at least 60–70 days.
6. **Pathway of infection**: Oral – by ingestion of 4-nuclei-containing cysts on contaminated food, contact to human feces, or intake of fecally contaminated drinking water. **Attention**: Flies may transport *Entamoeba* cysts (attached at their feet) from human feces to human food or even directly onto lips.
7. **Prophylaxis**: Avoid unwashed fruit in warm countries; use only clean (evtl. cooked) drinking water; keep away from human feces in nature.
8. **Incubation period**: 2–21 days for intestinal stages; liver abscesses mostly occur about 2–3 months after oral infection.
9. **Prepatency**: 2–14 days.
10. **Patency**: Eventually years.
11. **Therapy**: Drugs of choice are nitroimidazoles, since they show effects on stages occurring as well in the intestine as in the tissues; e.g. 3 × 500–750 metronidazole taken orally daily for 5–10 days (children 30 mg/kg bodyweight per day). In a considerable number of cases, cyst excretion persists without showing clinical symptoms of an entamoebiasis. Therefore stool examinations after treatment are recommended. In any way the oral application of 3 × 500 mg diloxanidfuroat for 10 days or paromomycin (3 × 500 mg/8–10 days) will stop

cyst excretion. In cases of massive bleedings, intestinal perforation, appendicitis and therapy-resistant amoebomas, chirurgical intervention is needed. **Attention**: Metronidazole and paromomycin are not allowed during pregnancy.

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3.10 Facultatively Pathogenic Amoebae

This are in principal free-living amoebae, which under some peculiar conditions may become pathogenic.

3.10.1 Species of the Genera *Acanthamoeba, Naegleria* and *Balamuthia*

1. **Name**: Greek – *acantha* = spine, thorn, *amoiba* = change; *Naegleria* originates from the family name of the Swiss scientist Naegler and *Balamuthia* was given in honour of the English parasitologist William Balamuth (1914–1981).
2. **Geographic distribution/epidemiology**: Worldwide, especially in eutrophic lakes; mainly weak (children) or immunosuppressed humans are severely infected, with even life-threatening cases; in general hundreds of thousands of people are infected every year.
3. **Biology, morphology**: In the last 20 years, more and more cases were reported, where humans showed infections due to such normally free-living amoeba. Infections apparently occurred in persons, who took their bath in warm swimming pools or in eutrophic lakes. Apparently the infections occur via the pharyngo-nasal region (via ductus olfactorius?). These amoebae are apparently able to invade the CNS, where they induce severe damages leading to death in a considerable number of immune-compromised humans. It is not clear why fully immunocompetent people remain uninfected or show only low-grade symptoms. It is still not understood why some strains of these protozoans become severely infectious and others not.

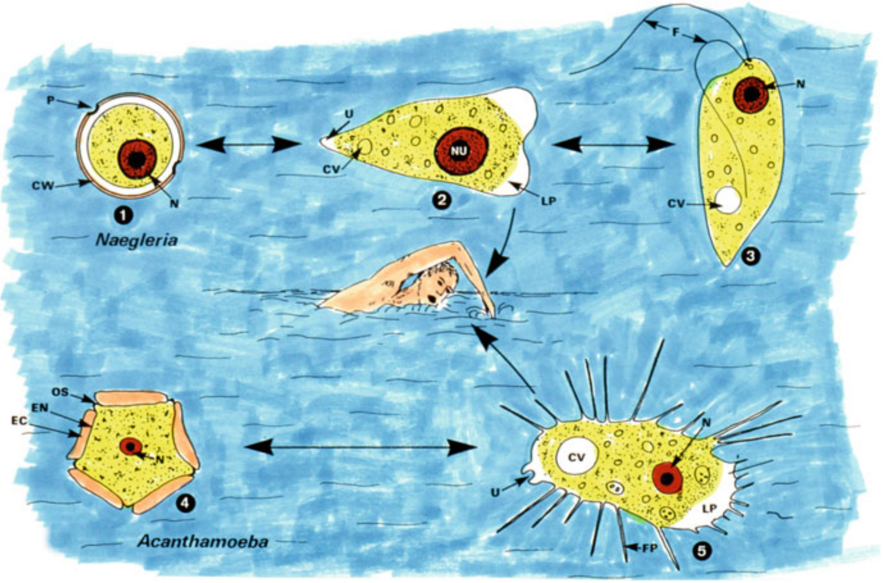

Fig. 3.22 Diagrammatic representation of the developmental stages of Naegleria and Acanthamoeba species. *CV* contractile vacuole; *CW* cyst wall; *EC* outer cyst wall; *EN* inner cyst wall; *FP* filopodium; *F* flagellum; *LP* lobopodium; *N* nucleus; *NU* nucleolus; *OS* ostiole; *P* pore; *U* uroid=posterior pole

After isolation from the fluid of infected patients, amoebae of the following genera were diagnosed:

(a) ***Acanthamoeba* species (e.g. *A. castellanii*)**

The isolated amoebae reached a size of up to 40 μm and are characterized by numerous very fine pseudopodia (=acanthopodia; Figs. 3.22, 3.23).

In the fluid as well as in lakes, cyst measuring 8–30 μm was detected. Their walls appear polygonal at their inner side. Similar amoeba stages, which were sometimes considered as *Hartmannella* sp. stages, were also isolated from the cornea of swimmers.

(b) ***Naegleria* species (*N. fowleri, N. gruberi*)**

The specimens of these species are found in the fluid as tiny (20 × 7 μm) amoebae, which are characterized by rather large (compared to the body size) hyaline pseudopodia. In lake water or in warm body cultures, they also produce 10–16 μm cysts as well as biflagellated stages (Fig. 3.22).

(c) ***Balamuthia mandrillaris***

This is a rather common species, which was first discovered in 1986 in the brain of a baboon that died in the San Diego Zoo, but is today also documented in HIV patients. The developmental stages measure 12–60 μm. They may be inhaled or can infect the body when entering wounds. Many symptomless persons showed, however, antibodies.

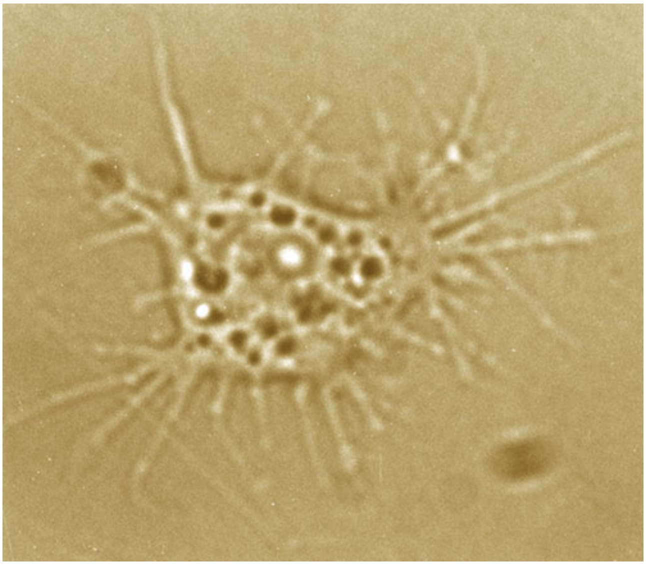

Fig. 3.23 Light micrograph of an Acanthamoeba stage showing the typical filopodia

4. **Symptoms of the disease**: In cases of infections with *Naegleria* species, symptoms of a meningoencephalitis are seen about 3–9 days after the supposed infection. However, the amoebae mostly had been found only *postmortem* during necropsies. Direct proofs can be obtained, when fluid of humans is injected into experimental animals. The disease is also called **primary amoebic meningoencephalitis (PAME)**. The symptoms are mostly very severe, so that without any medical treatment, infected persons die within 1–2 weeks after an infection. This was confirmed in experimental infections of monkeys. In contrast to such very severe symptoms due to *Naegleria* specimens, those of *Acanthamoeba* species are less dangerous, so that in these infections, death rates are much lower and a chronic process of the infection is predominantly running in many cases for several months. *Acanthamoeba* and *Balamuthia* species may induce a so-called granular amoebic encephalitis **(GAE)**. Their distribution among people using contact lenses is rather common, since these amoebae may reproduce and survive in the physiological storage fluids of such lenses. Conjunctivitis, keratitis and uveitis are thus rather common diseases. These species were also found in the cleaning waters of dental stools. All three genera (*Acanthamoeba*, *Balamuthia* and *Naegleria*) have developed species and/or strains which are very dangerous for immunosuppressed persons.
5. **Diagnosis**: Microscopic detection of trophozoites of these amoebae inside the cerebrospinal fluid obtained from infected humans or obtained after injection of infectious material into cultures. The microscopic investigation of fresh *Naegleria* stages shows significant high motility, while *Acanthamoeba* specimens (240 μm) move rather slowly, when fresh fluid is investigated.

Acanthamoeba stages can be cultured in various media. However, a quick diagnosis is needed; otherwise the patient may die before the test by help of cultures is finished.

Culture Methods

(a) ***Naegleria* spp.**
  - 2 % Bacto Agar (Difco) with heat-sterilized bacteria of the species *Aerobacter aerogenes*
  - 20 g Bacto Casitone to be mixed with 100 ml fresh, sterile horse serum within 1 l aqua dest

(b) ***Acanthamoeba* spp., *Naegleria* spp.**
  1. 1.5 g Agar to be diluted in amoeba medium and sterilized. Pages medium, which consists of 120 mg NaCl, 4 mg KH_2PO_4 and 1 l H_2O. This mixture remains active for 6 months, if it was sterilized in an autoclave for 15 min at 121 °C.
  2. The produced fluid should be cooled down to 60 °C and filled into plastic Petri dishes where they remain – if cooled – for about 3 months.
  3. 18–24 h old cultures of *E. coli* or *Aerobacter aerogenes* are added into 0.5 ml medium.
  4. Three to four drops of the suspended bacteria were placed onto the agar plate.
  5. Then the obtained brain puncture material (~0.5 ml) is dropped onto the agar plate and incubated at 37 °C.
  6. One week later stereo microscope investigations of the plate's surface for amoebae.

6. **Pathway of infection**: Nasal in the case of meningitis due to infection either with trophozoites = amoebic stages or cysts. Hard contact lenses may be contaminated with amoebae. An infection via air-transmitted cysts seems possible, but is not yet proven. *Acanthamoeba* stages are common in biofilms inside water transport systems. It was seen that these amoebae ingest *Legionella* bacteria and protect them from chemical cleaning products due to their ability to form within seconds a protecting cyst wall.
7. **Prophylaxis**: Avoidance to swim in eutrophic = plant rich lakes. Contact lens fluids should often be exchanged.
8. **Incubation period**: 1 day until 2 weeks.
9. **Prepatency**: 1 day until 2 weeks.
10. **Patency**: 3 weeks in case of *Naegleria* infections; several weeks in cases of untreated, chronic infection with *Acanthamoeba* spp.
11. **Therapy**
    1. In the case of **primary meningoencephalitis (PAME)** due to *Naegleria* species, a quick therapy with amphotericin B (daily 1 mg/kg bodyweight iv and 0.5–1 mg intrathecal or intrasternal) was successful. Combinations with rifampicin iv and miconazole iv efficacy were increased.

(2) In the case of **granulomatous encephalitis (GAE)** due to an infection with *Acanthamoeba* species, therapy should be done with pentamidine (4 mg/kg bodyweight), eventually in combination with ketoconazole and miconazole.

(3) In the case of *Acanthamoeba keratitis*, several persons underwent continuous topical treatment with propamidine isethionate, bacitracin/neomycin/polymyxin B and miconazole or clotrimazole. In cases of insufficient success of the above-described treatment, another additional systemic treatment should be used (itraconazole: 200 mg per day) or pentamidine (4 mg/kg bodyweight per day iv).

Further Reading

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Lorenzo-Morales J et al. (2013) Is *Balamuthia mandrillaris* a public health concern worldwide? Trend Parasitol 29:483–496.

Lorenzo-Morales J et al. (2015) An update on *Acanthamoeba* keratitis: diagnosis, pathogenesis and treatment. Parasite 22:10–17. doi:10.1051/parasite/2015010

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3.10.2 *Dientamoeba fragilis*

1. **Name**: Greek – *di* = double, *entos* = inner, *amoibos* = changing the shape; Latin: *fragilis* = fragile.
2. **Geographic distribution/epidemiology**: Worldwide, however, rather few documented cases in humans are published.
3. **Biology, morphology**: The trophozoites of *D. fragilis* (Fig. 3.24) occur in the colon of humans, reach a length of 4–12 µm and contain mostly two nuclei (provided with strolls of visible chromatin) and a large number of food vacuoles, which include bacteria and fungi. Reproduction occurs by binary fission. Cyst stages are unknown. Some authors include *D. fragilis* into the group of flagellates, since apparently two basal apparatus are seen during a defined period of the developmental cycle. This species was also diagnosed in high-grade primates in various Zoological gardens.
4. **Symptoms of the disease**: Under still unknown conditions, slimy feces were apparently induced together with phases of abdominal pain.
5. **Diagnosis**: In the case of microscopical investigations of fresh, unfixed feces, motile amoebae have been documented, while cysts were absent. Therefore

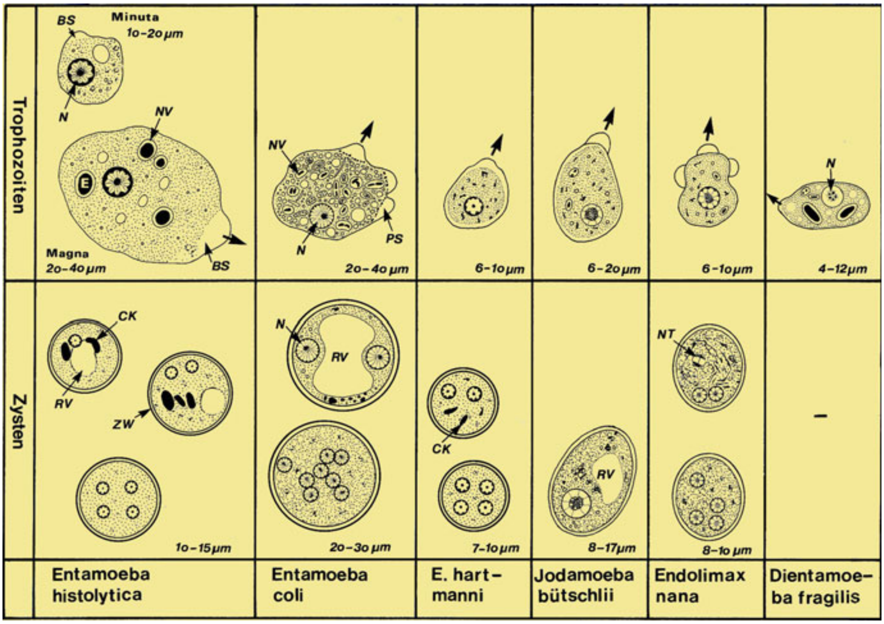
Trophozoiten
BS
Minuta
10-20 µm
N
NV
E
Magna
20-40 µm
BS
NV
PS
N
20-40 µm
6-10 µm
6-20 µm
6-10 µm
N
4-12 µm
Zysten
CK
RV
ZW
10-15 µm
N
RV
20-30 µm
CK
7-10 µm
RV
8-17 µm
NT
8-10 µm
–
Entamoeba histolytica
Entamoeba coli
E. hart-manni
Jodamoeba bütschlii
Endolimax nana
Dientamoeba fragilis

Fig. 3.24 Diagrammatic representation of common amoebae found in human intestine (shown in relation to their size); species diagnosis is based on the shape and position of the nucleolus; movement occurs in direction of the *arrows*. *BS* special pseudopodium (only one is formed); *CK* chromatidial body (reserve material); *E* erythrocyte of humans (enclosed in an food vacuole); *N* nucleus; *NT* nucleus during division; *NV* food vacuole; *PS* pseudopodia (in species where several are formed); *RV* vacuole containing reserve material (reacts on iodine coloration); *ZW* cyst wall

MIF and SAF methods show no stages. For fecal cultures, see *Entamoeba histolytica*.

6. **Pathway of infection**: Unknown; however, cysts might exist. Other authors discuss that amoeba stages might be included in *Enterobius vermicularis* eggs.
7. **Prophylaxis**: Avoidance of contact to human feces and of contact to monkey feces in zoological gardens.
8. **Incubation period**: Varying since parasite is only facultatively pathogenic.
9. **Prepatent period**: Days until weeks.
10. **Patency**: Months.
11. **Therapy**: Doxycycline (dosage like in the case of *Entamoeba histolytica*) (2 × 100 mg daily for 10 days), paromomycin (3 × 500 mg daily for 5–7 days) or iodoquinol (3 × 650 mg daily for 3 weeks).

Further Reading

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Crotti D et al. (2007) *Dientamoeba fragilis* in swine population. Vet Parasitol 145:349–351.

Munasinghe VS et al. (2013) Cyst formation and faecal-oral transmission of *Dientamoeba fragilis*. Int J Parasitol 43:879–883.

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3.10.3 Apathogenic Amoebae or with a Low-Grade Pathogenicity

In the colon of humans, several amoebae occur, which are considered as nonpathogenic or low-grade pathogenic. Some of them are listed here (Fig. 3.24):

(1) ***Entamoeba dispar, E. moshkovskii***

Both species look microscopically very similar to *Entamoeba histolytica* and range also in the size of this pathogenic species.

(2) ***Entamoeba coli***

This are 20–40 μm sized, slowly moving amoebae, which occur rather commonly. They possess 20–30 μm sized cysts, which contain mainly eight nuclei (but often also more). The nucleolus of the nuclei is situated not in the centre, while that of *Entamoeba histolytica* is always found there.

(3) ***Entamoeba hartmanni***

This species is characterized by its small size of only 6–10 μm in both stages (trophozoites, cysts). However, with respect to morphological aspects, it looks very similar to *E. histolytica* – especially the cysts which contain also always four nuclei. Some authors keep these stages also for *E. dispar* (see above).

(4) ***Entamoeba gingivalis***

This species is found in plaques in interdental spaces in the mouth of humans especially in cases of poor mouth hygiene.

(5) ***Endolimax nana***

The 6–10 μm sized trophozoites of this rather common species are mostly found motionless in the intestine of humans. Their cyst stage contains mostly four nuclei; however, also stages with 5–8 nuclei had been recorded in some publications. Cyst size is 8–10 μm.

(6) ***Iodamoeba butschlii***

This amoeba develops cysts which reach diameters of 6–17 μm and contain a large vacuole containing glycogen.

Further Reading

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Stensvold CR et al. (2011) Increased sampling reveals novel lineages of *Entamoeba*. Protist 162:525–541.

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3.11 *Isospora belli*

1. **Name**: Greek – *isos* = identical, *sporos* = cysts. Latin – *bellum* = belli.
2. **Geographic distribution/epidemiology**: Worldwide, it is estimated that several hundred million humans become repeatedly infected; the symptoms are called traveller's disease.
3. **Biology, morphology**: This coccidian species belongs to the phylum Apicomplexa (Sporozoa) and is characterized by a life cycle comprising asexual generations (**schizogony, sporogony**) and a sexual phase (**gamogony**), which runs inside vacuoles of epithelial cells of the human small intestine. All developments occur inside the host cell within a so-called parasitophorous vacuole. The oocyst is formed after the fusion of a motile male gamete (microgamete) with a large, nonmotile female one (macrogamete). The zygote develops a double-layered wall and thus becomes a so-called oocyst, which measures 25–35 × 18–20 μm in size. Inside these oocysts two sporocysts containing each four sporozoites are developed within about 3 days after the oocysts had been excreted within feces. In contrast to the oocysts of other species, those of *Isospora belli* are long ovoid (=laterally pressed, Fig. 3.25). In the case of sufficient humidity, these oocysts remain infectious for at least 1 year and also survive temperatures close to the freezing point.
4. **Symptoms of the disease (coccidiosis)**: Heavy infections and symptoms may occur 2 days after infectious oocysts are ingested during the ongoing phase of schizogony, leading to the destruction of numerous intestinal epithelial cells of the host. Their destruction may induce repeated fluid diarrhoeas, which may last several days up to weeks and are often accompanied by vomiting. In the case of HIV patients, symptoms may become life threatening. In the case of immunocompetent persons, infections may also introduce only low-grade symptoms. However, after 2–20 weeks, the symptoms may occur again. In the case of AIDS patients with severe symptoms, the parasites were not only found in the intestinal epithelial cells but also in lymph nodes far from the intestine (=disseminated stages) leading to organ-specific symptoms of disease.
5. **Diagnosis**: The oocysts can be diagnosed in the feces. In fresh stools they are unsporulated; in older ones they appear sporulated containing two sporocysts

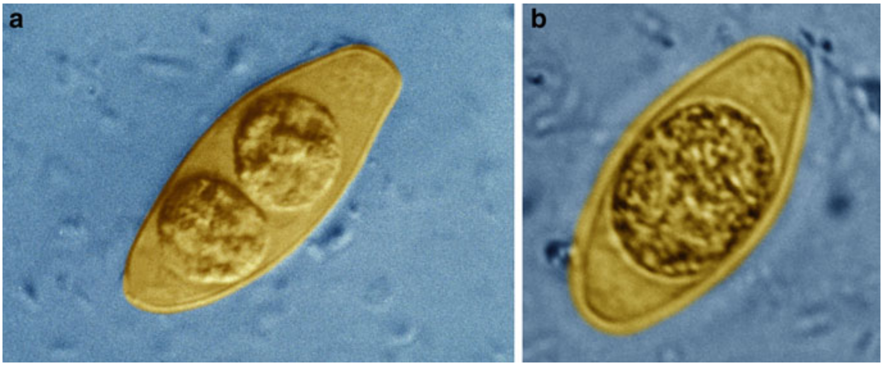

Fig. 3.25 Light micrographs of an unsporulated (**a**) and a sporulated oocyst of *Isospora belli* (**b**). The sporulated stage contains two sporocysts which each include four sporozoites

each with four sporozoites (Fig. 3.25). Recommended methods are flotation, SAF and MIFC. In cases of a detected blood eosinophilia, feces should be investigated, since the agents of traveller's disease may also induce this symptom.

6. **Pathway of infection**: Oral by ingestion of infections with oocysts contaminated food or drinking water.
7. **Prophylaxis**: Avoiding contact to human feces or uncooked contaminated drinking water.
8. **Incubation period**: 2–13 days, which correspond with the asexual phase in the intestine.
9. **Prepatent period**: 7–9 days.
10. **Patency**: 2 weeks up to 1–2 years (in the case of HIV patients).
11. **Therapy**: In the case of immunocompetent persons, the disease runs mostly self-limiting (especially in cases when persons drink sufficient water). However, cases of weak (children) or immunocompromised persons, symptoms of disease may become chronic. In these cases cotrimoxazole (4 × 800 mg sulfamethoxazole plus 160 mg trimethoprim) daily for 10 days and then 2× daily for 3 weeks are recommended. Also pyrimethamine (50–75 mg daily) is effective. In cases of HIV patients (endangered by phases of possible relapses), a long-lasting recidive-prophylaxis is recommended by application of cotrimoxazole at low dosages (e.g. 1 × 400 mg sulfamethoxazole/80 mg trimethoprim per day). In the USA HIV-infected persons had been successfully treated with diclazuril (1× daily 200 mg for 7 days). In the case that the above-cited treatment will not be well tolerated, the use of ciprofloxaxine (2× daily 500 mg for 7 days) is recommended.

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Ten Hove RJ et al. (2008) Real-time polymerase chain reaction for detection of *Isospora belli* in stool samples. Diagn Microbiol Infect Dis 61:280–283.

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3.12 *Cyclospora cayetanensis* (Cyclosporiasis)

1. **Name**: Greek – *kyklos* = spherical, round, *sporos* = spore, *cayetanensis* = Caribbean.
2. **Geographic distribution/epidemiology**: Worldwide some 100,000 humans with symptoms of disease.
3. **Biology, morphology**: Thirteen *Cyclospora* species have been described for vipers, moles, myriapods and rodents. Starting from the year 1985, increasing numbers of typical spherical oocysts were observed in the feces of immunocompetent and immunocompromised persons. Due to their small size (8–10 μm), unsporulated stages of this species were at first kept for stages of cyanobacteria and thus were described as **cyanobacteria-like bodies (CLB)**. Some authors kept these tiny oocysts for "large-sized" stages of the genus *Cryptosporidium*, which were also first detected in the same period. After intense light and electron microscopical studies, it was noted that this new species surely belongs to the Apicomplexa and that the infectious stage contains two sporocysts each with two sporozoites (Fig. 3.26). This species was placed in the genus *Cyclospora* and received the species name *cayetanensis*, since it was first described in the Caribbean region. The oocysts are excreted unsporulated within the feces. At temperatures of 25–32 °C, they sporulate and produce two sporocysts each containing two sporozoites of a length of up to 9 μm. These sporozoites are set free in the intestine of the next human hosts and probably enter the intestinal cells. However, details of the intestinal development are still lacking. Investigations of monkey feces (e.g. of chimpanzees) showed similar stages; however, infectivity for humans still remains to be proven.
4. **Symptoms of the disease (Cyclosporiasis)**: Immunocompetent as well as immunocompromised persons may be infected and then show the same leading symptoms: 3–4 times intermittent, watery diarrhoeas, which may persist for 2–9 weeks. These symptoms may also disappear without treatment. However, many patients show phases of strong abdominal pain and fatigue.

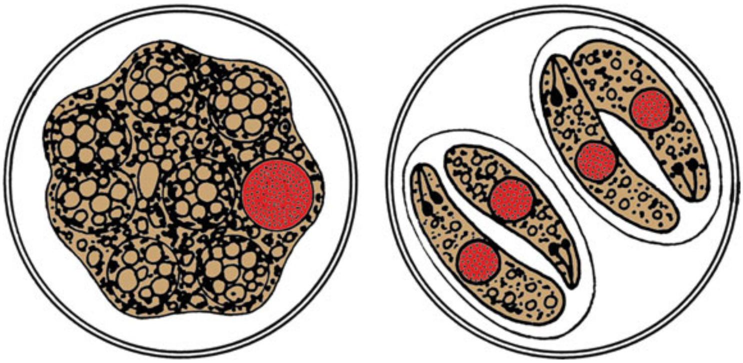

Fig. 3.26 *Cyclospora cayetanensis*. Diagrammatic representation of an unsporulated oocyst (*left*) and an oocyst with two sporocysts – each with two slender sporozoites containing a spherical, central nucleus

5. **Diagnosis**: Microscopical demonstration of the small-sized, pale-looking unsporulated oocysts of fresh human feces or sporulated stages in feces stored for several days (Fig. 3.26). When using the Ziehl-Neelsen method, these oocysts do not show the pink colour of the oocyst wall seen in *Cryptosporidium* oocysts. Using the epifluorescence method, the oocyst wall appears bluish.
6. **Pathway of infection**: Oral uptake of infectious oocysts with fecally contaminated food or drinking water.
7. **Prophylaxis**: Avoidance of potentially fecally contaminated raw food or drinking water, respectively, sites (e.g. toilets), where fecal remnants may be present.
8. **Incubation period**: 2–7 days.
9. **Prepatent period**: About 1 week.
10. **Patency**: Immunocompetent persons, 2 weeks; immunocompromised persons, 7–12 weeks.
11. **Therapy**: In the case of light symptoms, therapy is not needed. In severe cases the treatment using cotrimoxazole (2 × 800 mg sulfamethoxazole/160 mg trimethoprim daily) is very effective to stop diarrhoea. In the case of children, the diarrhoea and excretion of oocysts were stopped within 4 days by application of 5 mg (respectively, 25 mg) cotrimoxazole per kg bodyweight for 3 days. In another study the application of 5–25 mg/kg bodyweight of TMP-SMX for 3 days stopped the fulminant diarrhoeas.

Further Reading

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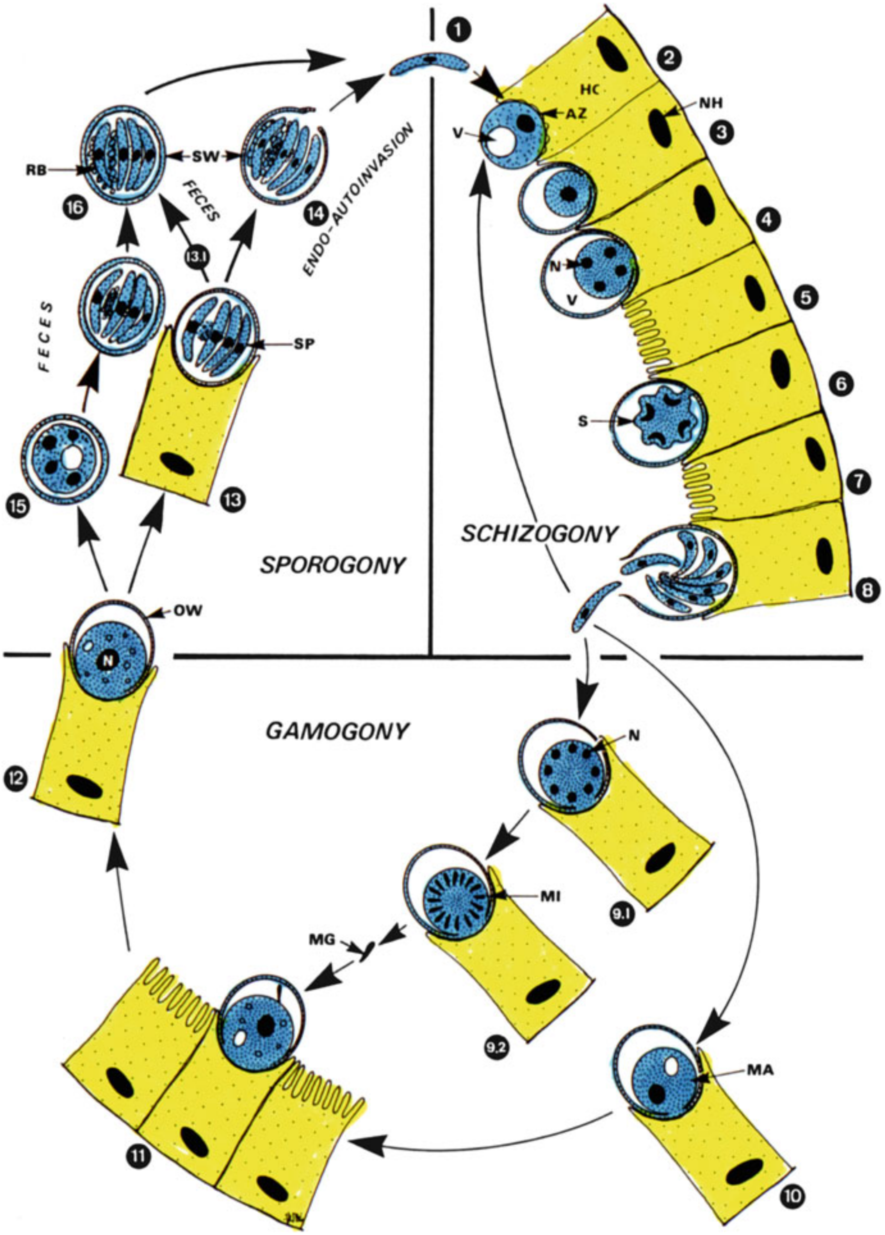
Ortega YRR, Sanchez R (2010) Update on *Cyclospora cayetanensis*. Clin Microbiol Rev 23:2018–234.

3.13 *Cryptosporidium* Species (Cryptosporidiosis)

1. **Name**: Greek – *kryptos* = hidden, *sporos* = seed, spore.
2. **Geographic distribution/epidemiology**: Worldwide reaching prevalence rates of 2.2 % in industrial states and up to 8.5 % in developing countries. Occasionally epidemics occur (e.g. in 1993 when more than 300,000 people were infected in Alabama due to contaminated drinking water).
3. **Biology, morphology**: There exists a broad spectrum of species which infect either both humans and animals together or singly (Table 3.5). The life cycle is diagrammatically depicted in Fig. 3.27. The cycle runs like a typical coccidian cycle except for the peculiarity that the development does not occur inside a parasitophorous vacuole in the interior of an epithelial cell of the host but just on the surface of an intestinal cell of the host. There the developmental stages are fixed among the microvilli of the host cell. The developmental stages are formed protruding into a vacuole which is formed and enlarged inside the parasitic stage (Figs. 3.27, 3.28, 3.29, 3.30).
4. **Symptoms of the disease (Cryptosporidiosis)**: This disease is a zoonosis, since the infection of humans may occur by uptake of the oocysts from other humans or from animal feces; both groups may infect themselves vice versa. Especially in immune-deficient persons, severe symptoms may occur leading to massive abdominal cramps and severe diarrhoeas. During these phases of diarrhoeas, up to 8 l of watery feces may be excreted containing millions of the very tiny, spherical oocysts (Fig. 3.28a), measuring only 5 μm in diameter. Especially children or weak immunocompromised persons may die from these severe water losses.

Table 3.5 Selected cryptosporidium species (genotypes)

Species/genotypes	Natural hosts	Main infested sites
C. hominis	**Humans**, monkeys	Small intestine
C. parvum	**Humans**, sheep, goats, **cattle**	Small intestine
C. suis	**Humans**, pigs	Small intestine
C. canis	**Humans**, **dogs**, foxes, coyotes	Small intestine
C. felis	**Humans**, cattle, **cats**	Small intestine
C. meleagridis	**Humans**, birds	Intestine
C. muris	**Rodents**	Stomach
C. bovis	**Cattle**, sheep	Small intestine
C. baileyi	**Chicken**, birds	Trachea
C. galli	**Chicken**, birds	Stomach
C. serpentis	**Snakes**	Stomach
C. molnari	**Saltwater fish**	Stomach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HC
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NH
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V
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V
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6
S
7
8
SCHIZOGONY
ENDO-AUTOINVASION
RB
SW
FECES
16
14
13.1
FECES
SP
13
15
SPOROGONY
OW
N
12
GAMOGONY
N
9.1
MI
MG
9.2
MA
10
11

Fig. 3.27 Diagrammatic representation of the life cycle of the species of the genus *Cryptosporidium*. The exact species determination is difficult since many species are not host specific and may introduce severe symptoms in several hosts. (**1**) Oral uptake of cysts containing four sporozoites which hatch inside the human intestine. (**2–8**) **Schizogony**: hatched sporozoites

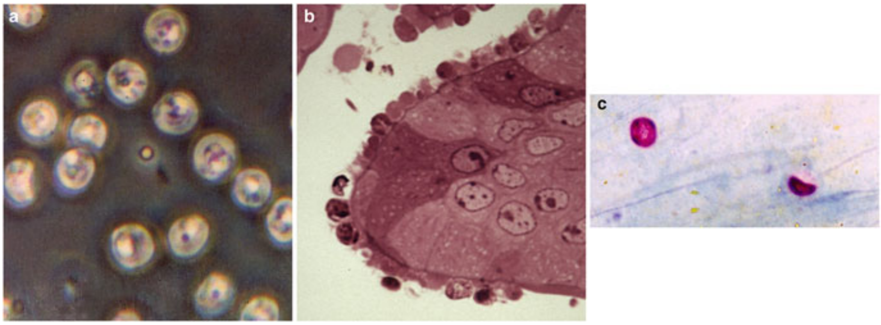

Fig. 3.28 Light micrographs of stages of *Cryptosporidium* species (**a**) oocysts isolated by flotation from feces; (**b**) section through the intestine of a mouse, showing numerous developmental stages attached to the epithelial cells of a mouse; (**c**) oocysts in a fecal smear preparation stained reddish with the help of the Ziehl-Neelsen method

5. **Diagnosis**: In fecal probes the very tiny oocysts are hardly recognized, even when using floating (sugar 300 g, aqua dest 320 ml, phenol 6.5 mg) MIFC of SAF-enrichment techniques. In smear preparations coloured according to Ziehl-Neelsen (test kits are commercially available), the oocysts appear by their reddish-pink colour (Fig. 3.28c).
6. **Pathway of infection**: Oral by uptake of sporulated oocysts which then contain four sporozoites. These oocysts can be found on contaminated vegetables, potatoes, seeds, etc. Other infections start during direct contact when investigating animal feces or human stool probes.
7. **Prophylaxis**: Children below 5 years and immunocompromised persons should avoid strictly any contact with feces of other persons or animals. Vessels or instruments that had contact with feces of any kind must be autoclaved or significantly sterilized with the help of UV light. **Attention:** According to the law to protect humans from infectious diseases, cases of human cryptosporidiosis must be announced to the governmental medical care authorities.
8. **Incubation period**: 1–2 days.

Fig. 3.27 (continued) become attached to the surface and develop after having transformed themselves into a spherical stage with an inner vacuole. The nucleus becomes repeatedly divided (**6**), and merozoites are formed protruding from the surface of the cytoplasm into the inner vacuole (**7**–**8**). After disruption this asexual reproduction is repeated several times (so that the microvilli of the intestine become closely covered (Fig. 3.28b). (**9**–**12**) **Gamogony**: during this phase, male (**9.1**, **9.2**) and female (**10**) gametes are formed which fuse and form a zygote (oocyst) which is covered by a protective wall (**12**). (**13**–**16**) **Sporogony**: inside the oocyst, the wall transforms, and finally four sporozoites are formed. The oocysts may stay inside the same host (and repeat the cycle) or are excreted with the feces. *AZ* attachment zone; *HC* host cell; *MA* macrogamete; *MI* microgamont, microgamete; *N* nucleus; *NH* nucleus of the host cell; *OW* oocyst wall; *RB* residual body; *S* schizont; *SP* sporozoite; *SW* wall of sporocyst; *V* inner vacuole

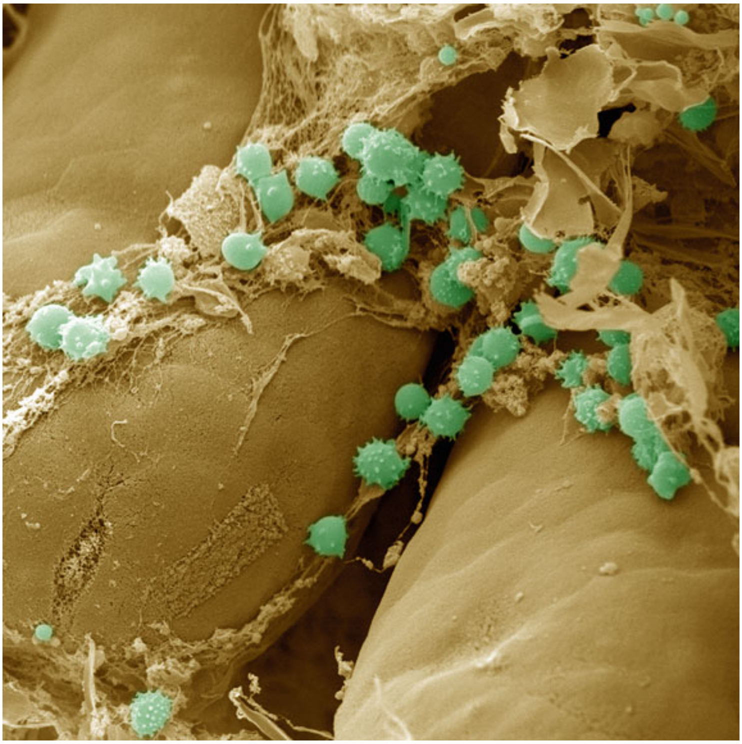

Fig. 3.29 Scanning electron micrograph of *Cryptosporidium* stages (*green*) attached at the remnants of the intestinal epidermal layer of a heavily infected mouse. Due to the effects of the parasites, most cells of the epithelial layer are deleted

9. **Prepatent period**: 2–4 days.
10. **Patency**: 12–14 days.
11. **Therapy**: An effective treatment registered at the governmental medical care authorities does not yet exist. Bovine colostrum (lactobin), paromomycin (2 g daily, orally), octreotide (up to 0.5 mg subcutaneously per day), spiramycin and azithromycin were used successfully in many cases. However, complete healing of HIV patients was not achieved. Nitazoxanide 3 × 500 mg daily in case of adults and 2 × 100 mg daily in the case of children reduced the symptoms significantly, but did not heal.

Further Reading

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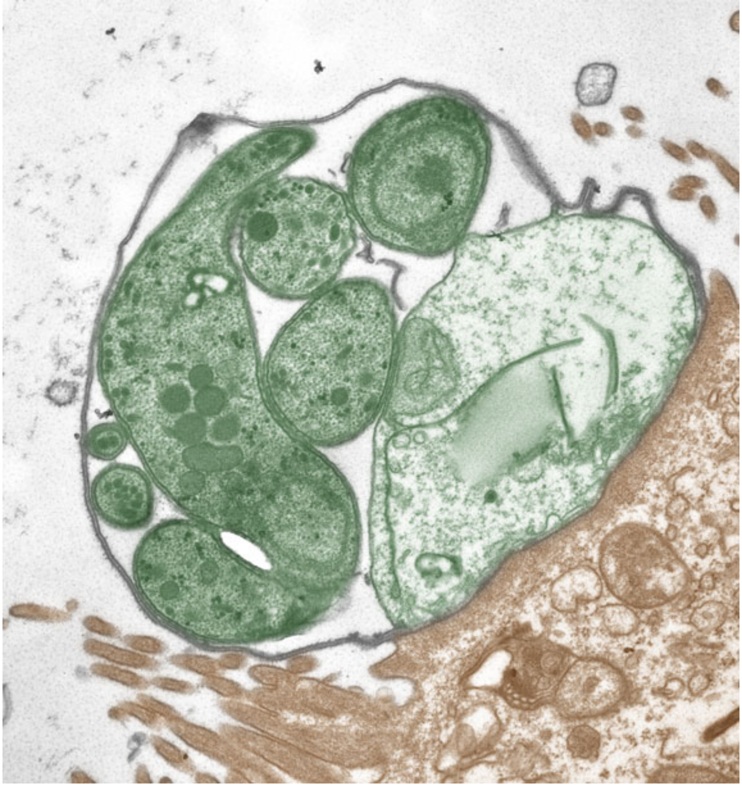

Fig. 3.30 Scanning electron micrograph of a section through a schizont of *Cryptosporidium parvum*, which is embedded into the microvilli of an intestinal cell. Note the residual body (*right*) and the sections through merozoites (*left*)

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3.14 Sarcosporidia

This group of Apicomplexa (Sporozoa) comprises several two-host species where the sexual stages are developed inside the intestine of predators and the asexual stages in the tissues of plant feeders or omnivores (Mehlhorn and Heydorn 1978). Table 3.5 shows examples of the numerous established life cycles. Figure 3.31 depicts important life cycles involving animals close to humans.

3.14.1 *Sarcocystis* Species Inside the Human Intestine (*S. suihominis, S. bovihominis*)

1. **Name**: Greek – *sarx* = meat, *kystos* = cyst. Latin: *sus* = pig, *homo* = human, *bos, bovis* = cattle, from cattle; Miescher's tubes = old name for *Sarcocystis* cysts honouring the Swiss biologist Friedrich Miescher (1811–1887), who detected and described such cysts inside the muscle fibres of mice.
2. **Geographic distribution/epidemiology**: Worldwide, there are apparently several hundred millions of humans infected (mostly probably without knowing it; symptoms are very low grade in immunocompetent persons).
3. **Biology, morphology**: Two *Sarcocystis* species (*S. bovihominis*, *S. suihominis*; Figs. 3.31, 3.32) may infect the subepithelial cells (lamina propria) of the small intestine of humans. There occurs the **gamogony** of their life cycle and also the **sporogony**, while the asexual **schizogony** and cyst formation occurs in intermediate hosts (=pigs or cattle) (Figs. 3.31, 3.32). Humans are infected by eating raw or undercooked meat of pigs (*S. suihominis*) or cattle (*S. bovihominis*). Within subepithelial cells gamogony starts with the formation of male and female gametes, which fuse, whereby a male gamete enters a host cell bearing a female gamont (Fig. 3.32), fuses with this stage thus giving rise to a zygote. This stage develops within 5–7 days an oocyst containing two sporocysts each with four sporozoites (Fig. 3.33a, b). As soon as this process is finished, the host cell is ruptured and releases the oocyst. Since the oocyst wall is very smooth, it becomes ruptured and releases the two small **infectious** sporocysts, which can be easily overlooked when examining fecal probes by light microscopy. The oocysts measure 20–25 × 12–15 μm, while the single sporocysts reach only a size of 14 × 8 μm (Fig. 3.33b).
4. **Symptoms of the disease (Sarcosporidiosis, coccidiosis)**: The severity of the symptoms depends on the amount of ingested cyst merozoites in raw or undercooked meat and on the species. *S. suihominis* (Fig. 3.32) is much more pathogenic than *S. bovihominis* (Fig. 3.31). In the case when large amounts of cyst merozoites have been ingested, severe symptoms of disease occur about 4–24 h after ingestion. They start with a phase of sweetening, freezing, vomiting, heavy diarrhoeas and intestinal cramps. The enormous loss of

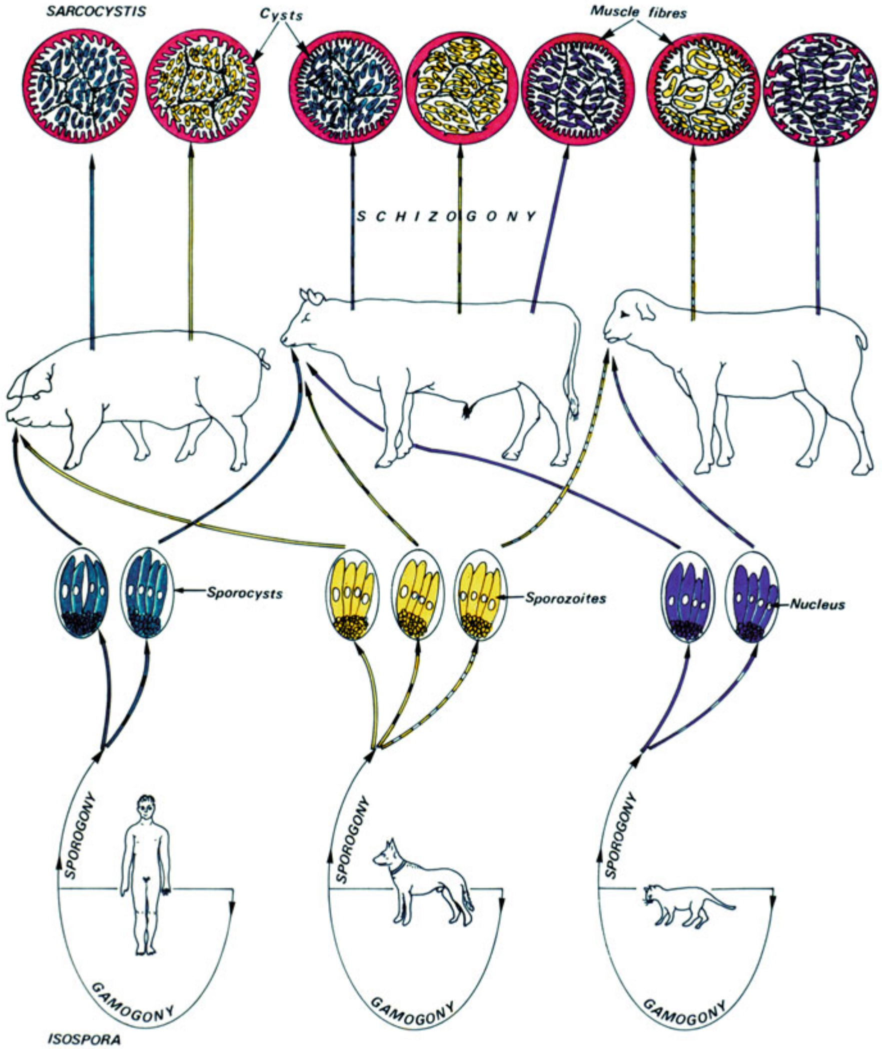
SARCOCYSTIS
Cysts
Muscle fibres
SCHIZOGONY
Sporocysts
Sporozoites
Nucleus
SPOROGONY
SPOROGONY
SPOROGONY
GAMOGONY
GAMOGONY
GAMOGONY
ISOSPORA

Fig. 3.31 Diagrammatic representation of the developmental cycles of the *Sarcocystis* species of humans and their closest house animals (after Mehlhorn and Heydorn 1978). Pigs, cattle and sheep are **intermediate hosts**. Humans, cats and dogs are **final hosts** which become infected by ingestion of meat containing sarcocysts. The species inside the final hosts are (from *left* to *right*) *Sarcocystis suihominis*, *S. bovihominis*, *S. bovicanis*, *S. ovicanis*, *S. bovifelis* and *S. ovifelis*.

water disturbs the balance of electrolytes, which may weaken the patient considerably. However, in general the symptoms decrease after 24 h without treatment.

5. **Diagnosis**: Microscopic detection of sporulated oocysts (Fig. 3.33a, b) and sporocysts inside fecal probes with the help of the floating method.

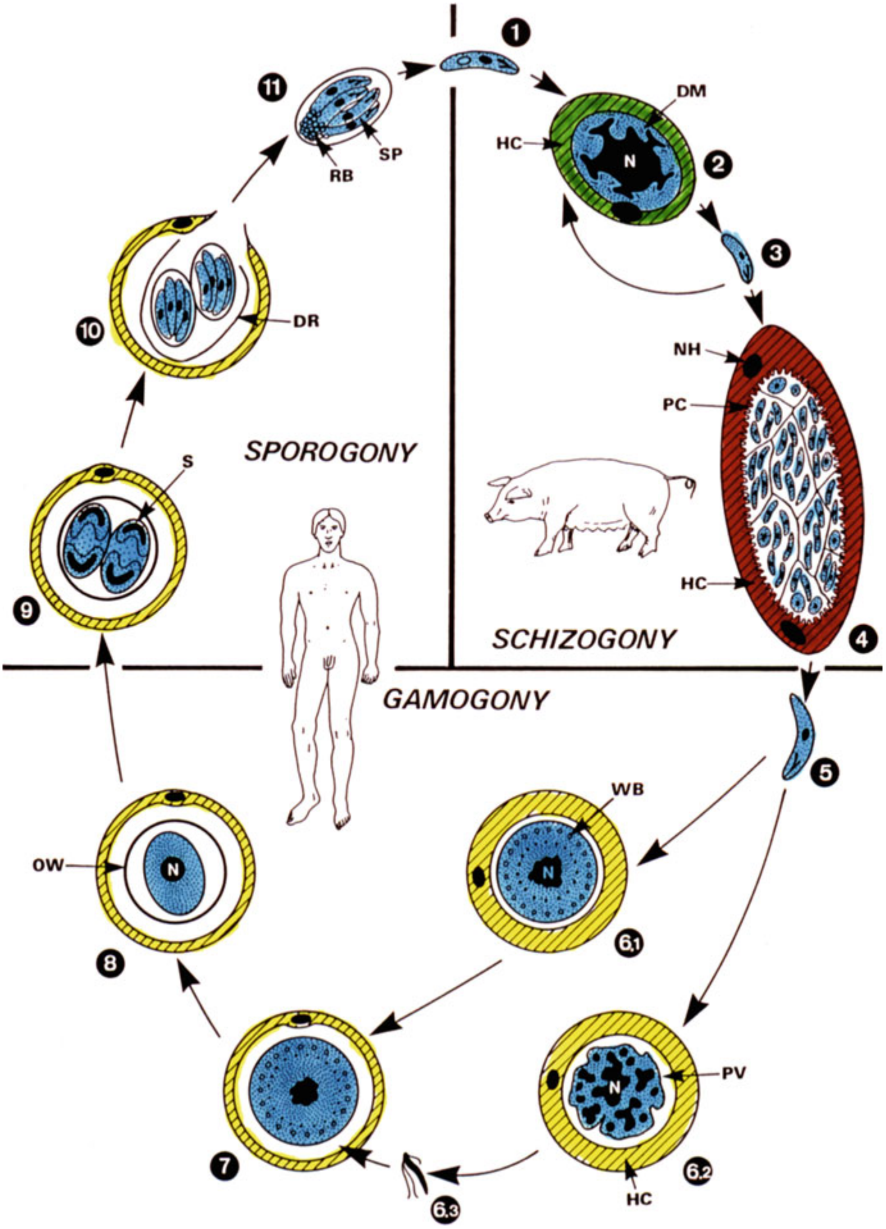

Fig. 3.32 Life cycle of *Sarcocystis suihominis*. (**1**) Motile sporozoites hatch from the ingested sporocysts inside the intestine of the intermediate host, i.e. pig. (**2**) Two generations of schizonts are formed (5–6 and 12–17 days after infection) inside endothelial cells of blood vessels, giving rise to 60–100 merozoites by endopolygeny. (**3**) Free motile merozoites; first-generation merozoites enter other endothelial cells and form schizonts, whereas merozoites of the second generation induce formation of tissue cysts. (**4**) Cyst formation inside typical cells (muscle fibres, brain cells); within these cysts, the parasites are reproduced by repeated endodyogeny leading to thousands of cyst merozoites which are situated inside chamber-like hollows. (**5**) When the final host man has eaten cyst-containing raw or insufficiently cooked meat, the cyst merozoites are set

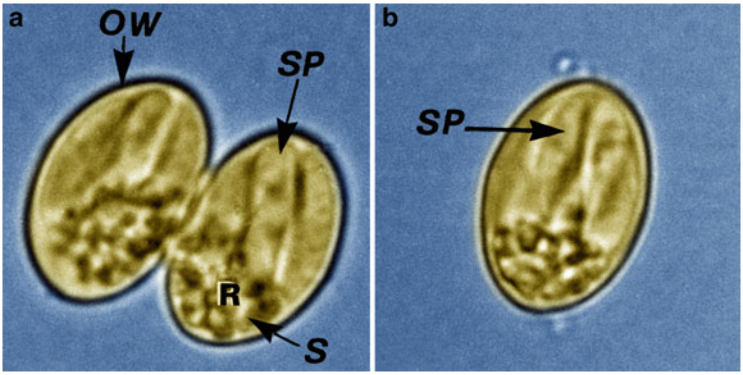

Fig. 3.33 Light micrographs of an infectious oocyst (**a**) and a sporocyst (**b**) of *Sarcocystis suihominis*. *OW* oocyst wall; *S* sporocyst; *SP* sporozoite

6. **Pathway of infection**: Oral uptake by ingesting raw or undercooked cyst-containing meat of pigs or cattle.
7. **Prophylaxis**: Eat only well-done meat.
8. **Incubation period**: 4–8 h.
9. **Prepatent period**: 5–10 days.
10. **Patency**: 6–8 weeks.
11. **Therapy**: Symptomatic replacement of water loss, collapse avoidance.

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Fayer R et al. (2015) Human infections with *Sarcocystis* species. CMR 28:295–315.

Gjerde B (2015) The resurrection of a species: *Sarcocystis bovifelis*. Parasitol Res. doi:10.1007/S00436-015—4785-4.

Harris VC et al. (2015) Human extraintestinal sarcocystosis. Curr Infect Dis Rep. doi:10.1007/s11908-015-0495-4.

Fig. 3.32 (continued) free and enter cells of the lamina propria. (**6**) Formation of female stages (macrogametes, **6.3**) via gamonts (**6.1, 6.2**) within 14 h after infection. (**7**) Fusion of gametes. (**8**) Formation of the oocyst wall around the zygote. (**9–11**) Formation of two sporocysts (containing four sporozoites each) inside the oocysts. The smooth oocyst wall often becomes disrupted. Thus, sporocysts are then found in the feces besides intact oocysts (**11**). *DM* developing merozoites; *DR* disrupted oocyst wall; *HC* host cell; *N* nucleus; *NH* nucleus of the host cell; *OW* oocyst wall; *PC* primary cyst wall; *PV* parasitophorous vacuole; *RB* residual body; *S* sporocyst; *SP* sporozoite; *WB* oocyst wall-forming bodies

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3.14.2 *Sarcocystis* Species in Human Muscles

1. **Name**: Greek – *sarx* = meat, *kystos* = cyst. Lindemann = German physician at the Russian Emperor's Court in the eighteenth century, first describer of sarcocysts in human muscles.
2. **Geographic distribution/epidemiology**: Apparently worldwide, however, probably mostly not diagnosed (Figs. 3.34, 3.35, 3.36).
3. **Biology, morphology**: In the muscles of humans and many monkeys, numerous cysts of the *Sarcocystis* type have been described in literature. These cysts had a size of about 120 × 70 μm and were thin-walled (Fig. 3.37). They contained long slender, banana-shaped cyst merozoites. The life cycle is unclear. It seems that humans may be accidental hosts of *Sarcocystis* species of monkeys (e.g. in Asia, Africa) and of life cycles of other *Sarcocystis* species in Europe and America.
4. **Symptoms of the disease**: Swellings in subcutaneous tissues, muscle pain and/or bronchospasms accompanied by fever and a high eosinophilia. Most cases, however, were detected by biopsy (due to other reasons) or in cases of postmortem inspections.
5. **Diagnosis**: Light microscopic investigation of muscle biopsy material (Fig. 3.37).
6. **Pathway of infection**: Apparently ingestion of infectious oocysts of a still unknown number of *Sarcocystis* species of animals.
7. **Prophylaxis**: Washing of vegetables and cooking of meat before eating.
8. **Incubation period**: Unknown.
9. **Prepatent period**: Probably 2–3 months like in other *Sarcocystis* species.
10. **Patency**: Unknown.
11. **Therapy**: Not defined, but sulfonamides and toltra- and ponazuril should be effective in cases with clinical symptoms.

Further Reading

Lindemann C (1863) Psorospermes chez l'homme. Bull Soc Imp Nat Moscow 36:425–436.

Mawia A (1990) Ultrastructure of the cyst wall of *Sarcocystis lindemanni* with pathological corrections. J Egypt Soc Parasitol 20:319–325.

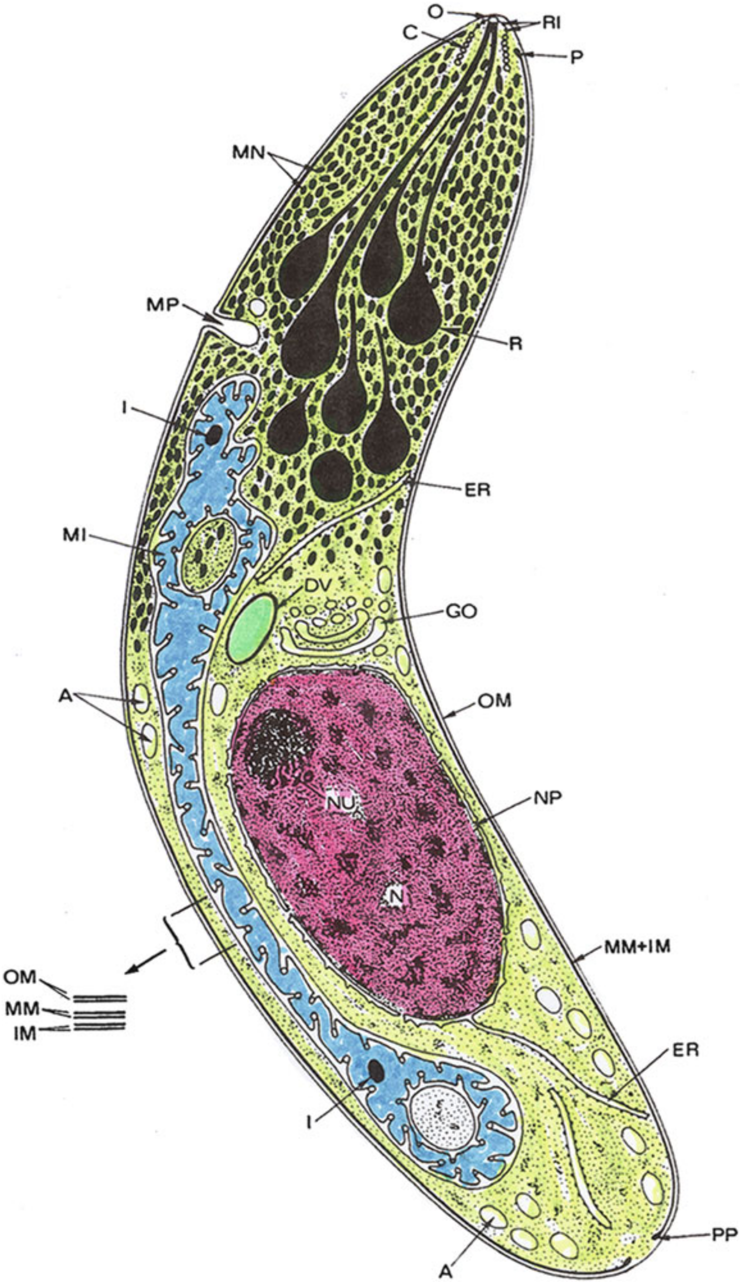


Fig. 3.34 Diagrammatic representation of the longitudinal section through a cystozoite (cyst merozoite) of *Sarcocystis* species, representing the basic appearance of the related stages of the genera *Toxoplasma*, *Besnoitia*, *Frenkelia*, *Hammondia*, *Isospora* and *Eimeria*. *A* amylopectin; *C* conoid; *D* dense, spherical bodies; *DV* double-walled vesicle; *ER* endoplasmic reticulum; *GO* Golgi apparatus; *I* dense inclusion; *IM* inner membrane; *MI* mitochondrion; *MM* middle membrane; *MN* micronemes; *MP* micropore; *N* nucleus; *NP* nuclear pore; *NU* nucleolus (karyosome);

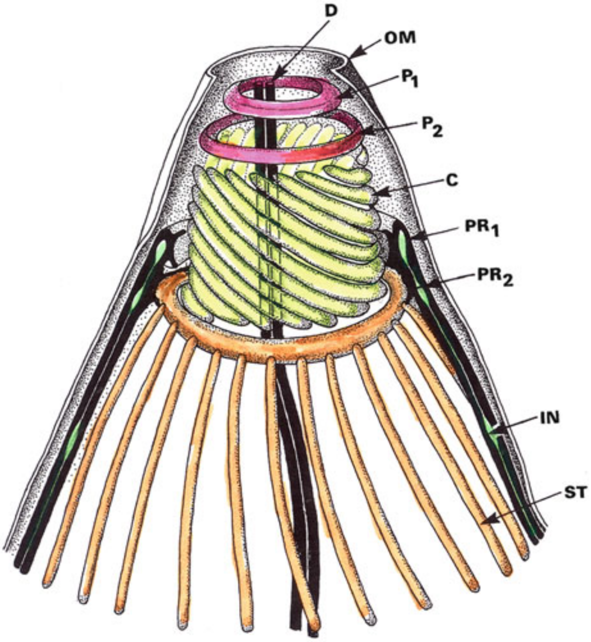


Fig. 3.35 Diagrammatic representation of the conoid

3.15 *Toxoplasma gondii* (Toxoplasmosis)

1. **Name**: Greek – *toxon* = bended, *plasma* = masses, structure. The genus name has its origin in the Latin name of the rodent species (*Ctenodactylus gundi*), where the agent of disease was detected by the French scientists Nicolle and Manceaux in the year 1907.
2. **Geographic distribution/epidemiology**: *T. gondii* are protozoans belonging to Alveolata (Sporozoa) and is distributed worldwide, reaching enormous infection rates in humans which increase during ageing. Thus this probably most common human parasite is found in 60–80 % of elder people worldwide. For HIV-infected persons as well as for other immunocompromised people, this parasite acts as "killer" number 3. Besides humans practically all warm-blooded animals may become infected, too.
3. **Biology, morphology**: The life cycle of this protozoan parasite runs facultatively. Final hosts are cats (house cats and species such as lions, tigers, etc.), which excrete unsporulated oocysts measuring 12 × 10 μm (Figs. 3.38, 3.41). During sporulation outside of the body, the oocysts develop inside two

◄

Fig. 3.34 (continued) O opening of the conoid; *OM* outer membrane of pellicle; *P* anterior polar ring; *PP* posterior polar ring; *R* rhoptries; *RI* ring-like elements of the conoidal canopy

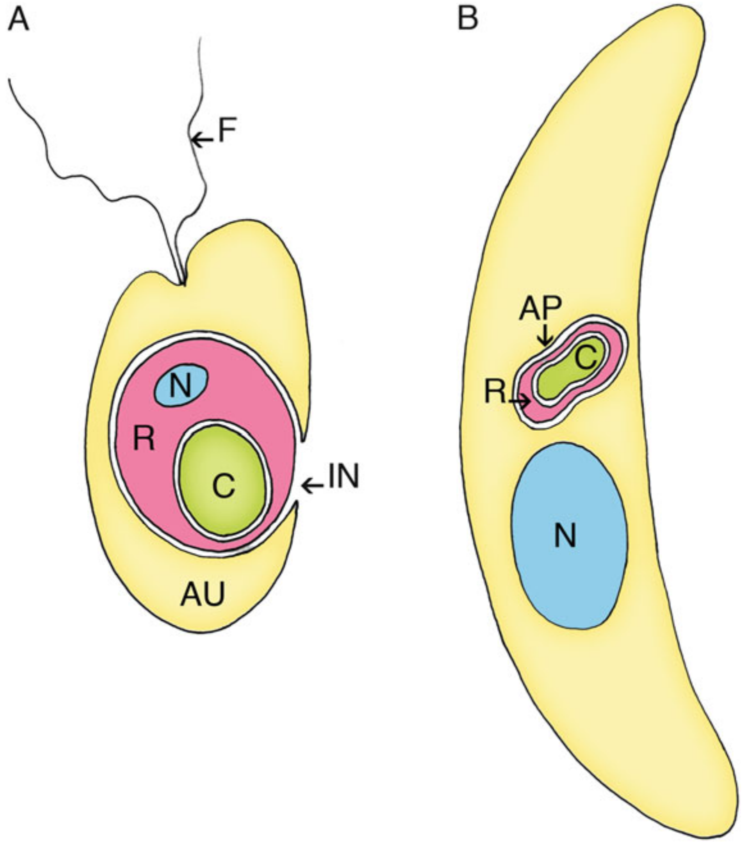


Fig. 3.36 Diagrammatic representation of the origin of the three genomes in coccidian zoites (*right*) and flagellates (*left*). *AP* apicoplast; *AU* autotroph flagellate; *C* cyanobacterium; *F* flagellum; *IN* invagination during ingestion; *N* nucleus; *R* rickettsial stage

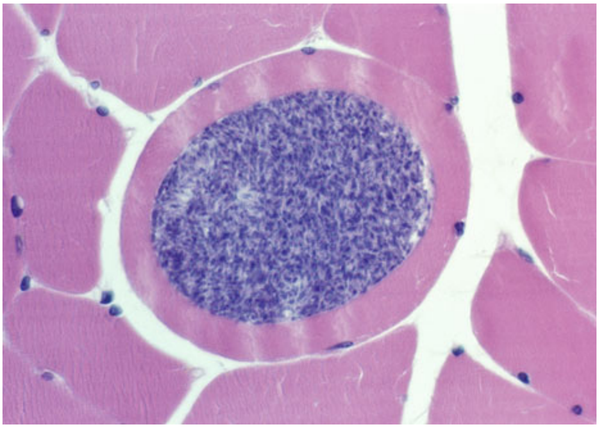


Fig. 3.37 Light micrograph of a coloured section of a *Sarcocystis* cyst inside a muscle fibre of a man

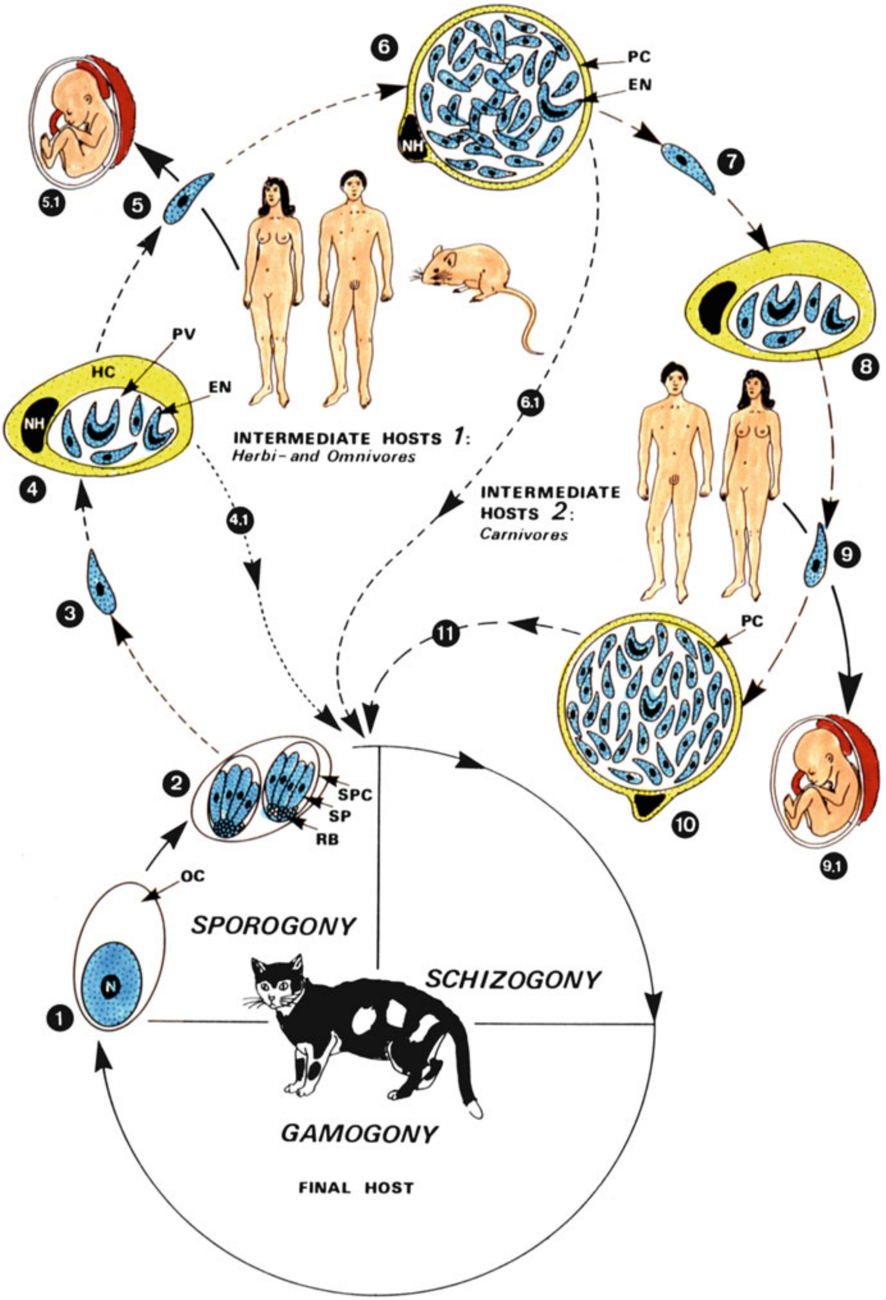

6
PC
EN
NH
7
5.1
5
8
PV
HC
EN
NH
INTERMEDIATE HOSTS 1:
Herbi- and Omnivores
6.1
4
4.1
INTERMEDIATE HOSTS 2:
Carnivores
9
3
11
PC
2
SPC
SP
RB
10
9.1
OC
SPOROGONY
N
1
SCHIZOGONY
GAMOGONY
FINAL HOST

Fig. 3.38 ***Toxoplasma gondii***. Life cycle and transmission pathways of *Toxoplasma gondii*. The typical life cycle proceeds in the intestinal epithelium of felids (final host) which are infected by oral uptake of sporulated oocysts (**2**), ingestion of “pseudocysts” (**4.1**, **8**) or tissue cysts (**6.1**, **11**) with meat of various intermediate hosts (of 2 types). (**1**) Unsporulated oocysts are excreted with feces. (**2**) Sporulation (i.e. formation of sporocysts and sporozoites) occurs outside the final host. These stages may become spread by transport hosts such as flies and cockroaches. (**3**) After

sporocysts, each finally containing four sporozoites. These stages are infectious for intermediate hosts, which get in contact with feces of felines. In humans and in many slaughter animals, the parasites (sporozoites) enter first into the cells of the reticuloendothelial system (RES), where they start to be surrounded and thus protected inside parasitophorous vacuoles and undergo repeated binary fissions (**endodyogeny**). During this process two daughter cells are de novo developed inside a mother cell (Figs. 3.38, 3.39a). These daughter cells are also described as **tachyzoites** (Greek: *tachys* = quick), since they develop very quickly and enter other host cells. They reach a length of about 6–7 μm (Fig. 3.39a, b). During this phase of very quick reproduction, the **tachyzoites** are found in many organs but also inside lymph nodes and in the fluid cerebrospinalis. Finally they enter muscle and brain cells and are now called **bradyzoites** (Greek: *bradys* = slow). In this stage the host cells develop themselves into so-called tissue cysts, which reach a size of 50–300 μm in diameter (Fig. 3.39c, d). If cats ingest such cysts within raw meat, they start again the production of infectious oocysts (Figs. 3.38, 3.40, 3.41).

4. **Symptoms of the disease (Toxoplasmosis)**: In most cases, i.e. in healthy persons, toxoplasmosis is mostly not noted, since the symptoms are unspecific and of low grade (e.g. weakness, pain in arms and legs, etc.). However, serologic investigations show that with the increasing age of persons, the rate of infections increases. Besides these common, unspectacular symptoms under special conditions, *Toxoplasma gondii* infections may become harmful reaching the status of a severe disease:
   (a) **Acquired postnatal infection**

   This disease is acquired by ingestion of sporulated oocysts excreted by cats or by ingestion of undercooked raw meat of infected vertebrates. After an incubation period of about 2–3 weeks, the following symptoms can be observed:

Fig. 3.38 (continued) ingestion of oocysts by intermediate hosts of type 1, the sporozoites are set free inside its intestine and penetrate numerous types of extraintestinal cells (i.e. cells of the RES). (**4**) Inside the host cell the parasites reproduce by a typical binary fission (endodyogeny) leading to "pseudocysts" which are filled with merozoites (i.e. **tachyzoites**). (**4.1**) After ingestion of such pseudocysts, cats may become infected. (**5**) Free merozoite (tachyzoite) in blood or lymph fluid after bursting of a pseudocyst. (**5.1**) When the first infection is in pregnant women (or animals), these merozoites may pass into the placenta and infect the foetus, leading to severe damage. (**6**) Formation of **tissue cysts**, mainly inside brain and muscle cells. After several endodyogenies these cysts (waiting stages) contain numerous cyst merozoites (**bradyzoites, cystozoites**) which are infectious for cats (**6.1**). (**7**–**10**) When carnivorous animals or man (intermediate host of type 2) ingest such tissue cysts (**10**) as in intermediate hosts of type 1, diaplacental transmission (**9.1**) may also occur (see Fig. 5.1), leading to congenital toxoplasmosis. (**11**) Cats may also become infected by ingestion of tissue cysts from type 2 intermediate hosts. Then they pass oocysts after 3–5 days, whereas this prepatent period is longer after inoculation of pseudocysts (9–11 days) or oocysts (21–24 days). *EN* division by endodyogeny; *HC* host cell; *N* nucleus; *NH* nucleus of host cell; *OC* oocyst; *PC* primary cyst wall; *PV* parasitophorous vacuole; *RB* residual body; *SP* sporozoite; *SPC* sporocyst

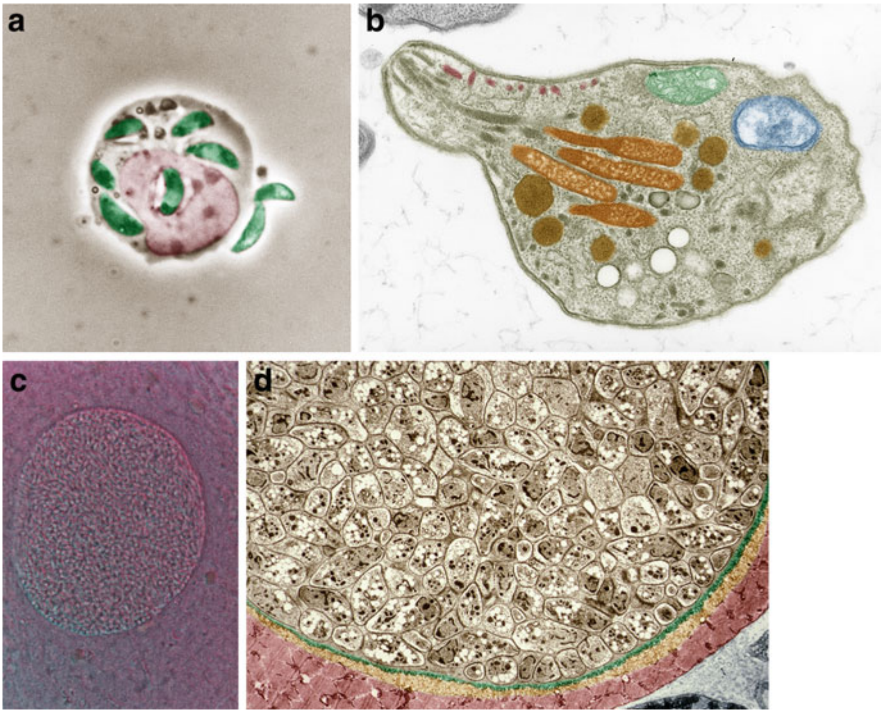


Fig. 3.39 Light microscopic photos (**a**, **c**) and electron micrograph (**b**, **d**) of stages of *Toxoplasma gondii*. (**a**) Macrophage containing within parasitophorous vacuoles penetrated tachyzoites. Two further tachyzoites start their penetration process. (**b**) Protruded anterior end of a tachyzoite showing the typical organelles such as conoid, rhoptries and micronemes. The section of the tubular mitochondrion is coloured in green, while the apicoplast is blue stained. (**c**) *Toxoplasma* cyst in the brain filled by bradyzoites. (**d**) Section through periphery of a *Toxoplasma* cyst in a muscle fibre. The interior shows sections of bradyzoites. The *green layer* represents the amorphic peripheral cyst material. The *yellow material* represents degenerated muscle cell material, which covers the single limiting membrane of the cyst. The *reddish stained layer* represents the muscle elements (myosin, etc.)

- Swellings of lymph nodes (adenitis)
- Infections of the eyes (iridocyclitis, chorioretinitis)
- Infections of the brain (meningoencephalitis),
- Infection of visceral organs (e.g. leading to intestinal pneumonia, hepatitis, myocarditis, enterocolitis, myositis, oedema of the skin)

(b) **Connatal (congenital) toxoplasmosis**

If the foetus inside a woman becomes infected for the first time, it is highly endangered. In Germany about 6000–7000 of such cases occur per year. In about 50 % of these cases, the parasites enter the foetus so that about 1500 foetuses per year suffer from slight to severe symptoms of a toxoplasmosis. In such cases the above-listed organs may be affected, so

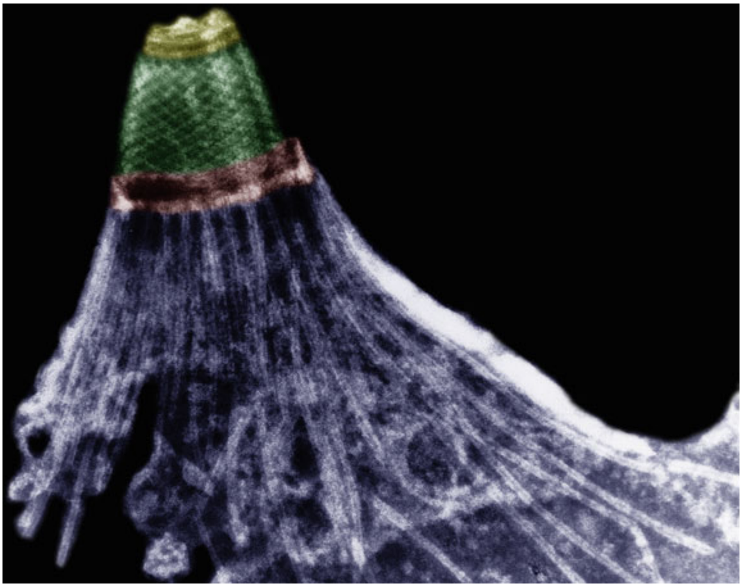


Fig. 3.40 Negatively stained electron micrograph of the anterior pole of a tachyzoite of *Toxoplasma gondii* showing the conoid (*green*), the two polar rings (*brown*), at which the subpellicular microtubules are attached. The covering pellicle has been discharged during preparation

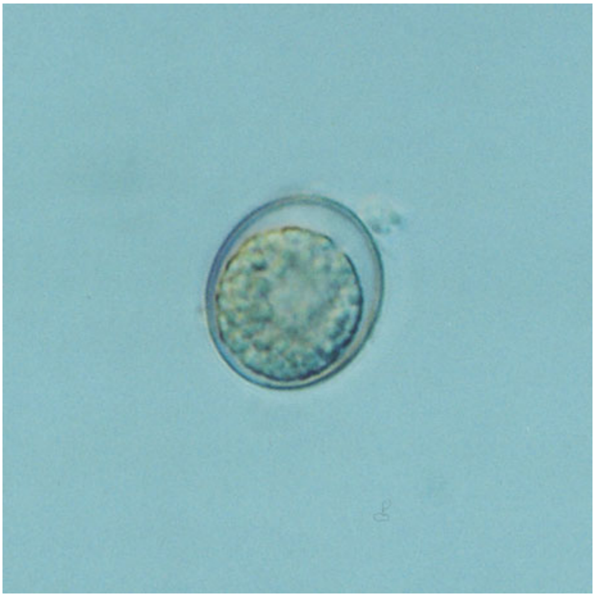


Fig. 3.41 Light micrograph of an unsporulated oocyst of *Toxoplasma gondii* obtained from fresh cat feces

that severe fetopathias may be introduced. Also early birth or abortus may occur. Toxoplasmosis obtained as a baby may even induce 20 years later severe symptoms such as loss of eye functions.

5. **Diagnosis**: Acute *Toxoplasma* infections may be diagnosed by detection of parasites (tachyzoites) in blood, lymph node punctions, in fluid or in biopsies of tissues. For the determination of the age of an infection, serological tests are used, which can be done by examination of the presence of the different antibody classes. **Fresh infections** are indicated by the early presence of the **IgM class**. If these antibodies are lacking or occur in lower numbers than those of the **IgG class**, an older infection is present.

   IgM antibodies can be diagnosed by the following tests:
   - Double-sandwich IgM-ELISA (**DSIgM-ELISA**)
   - Reverse-enzyme immunoassay (**REIA**)
   - Immunosorbent agglutination assay (**ISAGA**)
   - Enzyme immunoassay (**EIA**)

   The following tests show an infection of about 1 year. The IgG antibodies can be demonstrated by the following tests:
   - Complement binding reaction (**KBR**)
   - Colouring according to Sabin and Feldman test (**SFT**)
   - Indirect immunofluorescence test (**IIFT**)
   - Enzyme-linked immunosorbent assay (**ELISA**)
   - Direct agglutination test (**DAT**)

   Determination of a first infection of a pregnant woman

   The seroconversion is the essential marker. Thus it is needed to control monthly the blood status of a *Toxoplasma*-seronegative pregnant women, since fresh first infections need treatment. Within this context it is needed to evaluate and interpret the antibody reactions:
   - *Toxoplasma* antibodies are noted with the help of the IIFT-test system already 11 days after the infection and reach their highest levels after 3–4 weeks (like those in SAF-tests).
   - Significant IgG levels, absence of IgM antibodies and KBR-titres of $\geq$1:10 indicate an acute toxoplasmosis.

   Attention: Variations of the antibody titres may be based on physiological reactions and on the methods of analysis. Thus repetitions of the tests are recommended.

6. **Pathway of infection**: With respect to the complicated life cycle of this species, several possibilities exist to get infected with *Toxoplasma gondii*. **Infections** may occur:

   (a) By ingestion of sporulated oocysts originating from cat feces, cat fur or contaminated food

   (b) By oral uptake of stages in tissue cysts within muscles of infected animals in case the meat is eaten raw or undercooked

   (c) By intrauterine passage from mother to foetus (often in several regions, 1 % of the newborn babies are already infected)

   (d) By blood transfusions (this pathway occurs in rather few cases due to the fact that tachyzoites occur only in very low numbers in blood)

7. **Prophylaxis**: Very young children, pregnant women (in case they are still seronegative for *Toxoplasma*) and immunosuppressed persons should avoid contact to cats and cat feces and should not eat raw or undercooked meat. Deep freezing of meat at −20 °C for at least 24 h and preparation of meat at at least 54 °C will potentially kill *Toxoplasma* stages inside the meat. Cats in own household should not be fed with raw meat. **Important**: Pregnant women should be tested for *Toxoplasma* antibodies at the very beginning of the pregnancy. In case there are no existing *Toxoplasma* antibodies, this test must (!) be repeated at each of the following monthly investigations.
8. **Incubation period**: Hours up to 2 days in cases of acute toxoplasmosis.
9. **Prepatent period**: Depending on the pathogenicity and virulence of the *Toxoplasma* strain: 1–2 days up to several weeks.
10. **Patency**: Years, tissue cysts may exist for years within tissue cells without any symptoms. In cases of ruptures of these cysts, new phases of infections of other cells may occur (see chronic toxoplasmosis).
11. **Therapy**

    (a) **Congenital toxoplasmosis**

    The treatment is recommended not only in cases of existing symptoms but also in an asymptomatic congenital toxoplasmosis (detected accidentally in serotests) in order to avoid later toxoplasmosis symptoms.

    - **Pyrimethamine** 1 mg/kg bodyweight every 2 days (in cases of severe organ infection 2 mg for 3 days) combined with sulfadiazine (2 × 50 mg/kg bodyweight daily). In addition application of 5 mg folinic acid for 2 days and control of the blood composition and amount of thrombocytes. **Duration of chemotherapy**: In cases of asymptomatic infections, 6 months; in cases of defined clinical symptoms, 12 months.
    - **Spiramycine** (100 mg/kg bodyweight daily in two to three portions) is recommended in cases that the above-described treatment is not tolerated, and the literature recommends the following treatment. In cases of clear CNS symptoms and/or chorioretinitis inclusive macular damages, it is recommended to give additionally **prednisolone** (1–2 mg/kg bodyweight) until inflammation symptoms decrease.

    (b) **Postnatal toxoplasmosis in the case of immunocompetent persons**

    Low-grade symptoms and noncomplicated lymphadenopathy do not warrant treatment, which, however, is recommended in cases of encephalitis, myocarditis, chorioretinitis, etc. or in cases with strong persistent general symptoms. The standard therapy is the following: **Pyrimethamine** 2 × 100 mg on day 1 (children 2 mg/kg bodyweight), followed by daily 20–50 mg (children 1 mg/kg bodyweight) combined with **sulfadiazine** 4 × 500–1000 mg daily (children 50–100 mg/kg bodyweight) and in addition folinic acid (10 mg daily, blood control needed).

    Length of treatment: 2–6 weeks (in cases of chorioretinitis 4 weeks).

Since in the case of chorioretinitis blindness may occur, it is recommended to give additionally **prednisolone** (1–2 mg/kg bodyweight, daily).

(c) **Toxoplasmosis during pregnancy**

Therapeutic approaches should only be done in clear documented cases. Beginning at the 20th week of pregnancy, pyrimethamine (50 mg on the first day, followed by 25 mg daily) should be given plus standard sulfadiazine and folinic acid (under blood status control). Treatment should be done in 3–4 of 1-week-long treatment cycles interrupted by 4–6-week-long intervals until the birth of the baby. Before the 20th week and in cases that pyrimethamine is not accepted, spiramycine may be applicated (3 g = 9 mio I.E.) daily divided into 3–4 doses until birth.

(d) **Toxoplasmosis in the case of immunocompromised persons**

If by computer tomography typical symptoms have been proven (e.g. encephalitis, hypodense regions, hollows inside the brain, etc.), therapy should be started as soon as possible. **Treatment** should be done by application of **pyrimethamine** (first day 200 mg, followed by 75 mg (25–100 mg) daily plus **sulfadiazine** 4 g (2–6) daily in four divided doses. These compounds are applicated for at least 3 weeks – depending on the severity of clinical symptoms.

In the case of **sulphonamide intolerance**, pyrimethamine might be combined with **clindamycin** (4 × 600 mg daily). **Atovaquone** (4 × 740 mg daily) and azithromycin/pyrimethamine have been tested in pilot studies and showed high efficacy. Due to the high rates of possible recidives after a successful treatment, it is needed to add a so-called secondary prophylaxis. This can be done by ingestion of 25–50 mg pyrimethamine plus 2–4 g sulfadiazine per day or by pyrimethamine alone (50–75 mg daily). Less effective is the ingestion of dapsone, cotrimoxazole or clindamycin. The combination **epiroprim** and **dapsone** showed in animals a very good efficacy with respect to the elimination of *Toxoplasma gondii* stages and showed at the same time good effects against bacteria.

Further Reading

Blader IJ et al. (2015) Lytic cycle of *Toxoplasma gondii* 15 years later. Annu Rev Microbiol 69:463–485.

Guo M et al. (2015) Prevalence and risk factors for *Toxoplasma gondii* infection in meat animals and meat products destined for human consumption. J Food Prot 78:457–476.

Hakimi MA, Bougdour A (2015) *Toxoplasma*'s way of manipulating host transcriptome via secreted effectors. Curr Opin Microbiol 26:24–31.

Pittman KJ, Knoll LJ (2015) Long-term relationships: the complicated interplay between host and the developmental stages of *Toxoplasma gondii* during acute chronic infections. Microbiol Mol Biol Rev 79:387–399.

Wei HX et al. (2015) A systematic review and meta-analysis of the efficacy of anti-*Toxoplasma gondii* medicines in humans. PLoS One. doi:10.1371/journal.pone.0138204.

Wyrosdick HM, Schaefer JJ (2015) *Toxoplasma gondii* history and diagnostic test development. Anim Health Res Rev. doi:10.1017/S466252315000183.

3.16 *Plasmodium* Species (Malaria)

1. **Name**: Latin, Italian; *malum* = bad, *evil* = not fresh, *aria* = air. French: *paludisme* = swamp, fever. German: *Wechselfieber* = changing fever.
2. **Geographic distribution/epidemiology**: Malaria occurs in countries with high heat and humidity being situated between 40° North and 30° South. About 200 million people are constantly infected worldwide; 1 billion are endangered; still today 700,000 up to 1 million people die each year (mostly children).
3. **Biology, morphology**: The agent of malaria is a protozoan organism belonging to the group of Sporozoa (Apicomplexa, Alveolata). It is transmitted to humans by the bite of female mosquitoes of the genus *Anopheles*. There are no animals as reservoir hosts besides humans. An infection may also occur through the use of infectious blood conserves, since *Plasmodium* stages stay alive in cooled blood for at least 2 weeks. Transmission is also possible using contaminated drug injection needles. Agents of malaria may also become transmitted from the mother to her unborn child by placenta passage or during birth (connatal malaria). A natural way of transmission happens in the case of the so-called airport malaria, which mostly afflicts workers at airports, when infected *Anopheles* mosquitoes arrive in a plane from endemic countries. The infectious stages (sporozoites) are transmitted within the saliva of the female mosquito during its blood meal. At first the parasites multiply asexually in the parenchymal cells of the liver and of the RES (reticuloendothelial system) in the phase of the so-called exoerythrocytic schizogony. After 1–6 weeks (depending on the *Plasmodium* species!), the asexual stages in the liver (the so-called merozoites) enter the red blood cells. **Prepatency** defines the time from the infection to the first occurrence of stages in the blood cells. **Incubation period** is different: it defines the period from the infection to the occurrence of the first symptoms. After penetration into an erythrocyte (Figs. 3.42, 3.53) the **merozoite** at first appears as a small trophozoite described as a **signet ring stage**. Its large digestion vacuole in the centre of the cell is not stained and pushes the nucleus and cytoplasm aside. Thus only the stained cytoplasm at the periphery of the parasite appears as a ring and the coloured nucleus as a precious stone. Thus this early stage is a very characteristic sign of the early malaria (Figs. 3.43, 3.44).

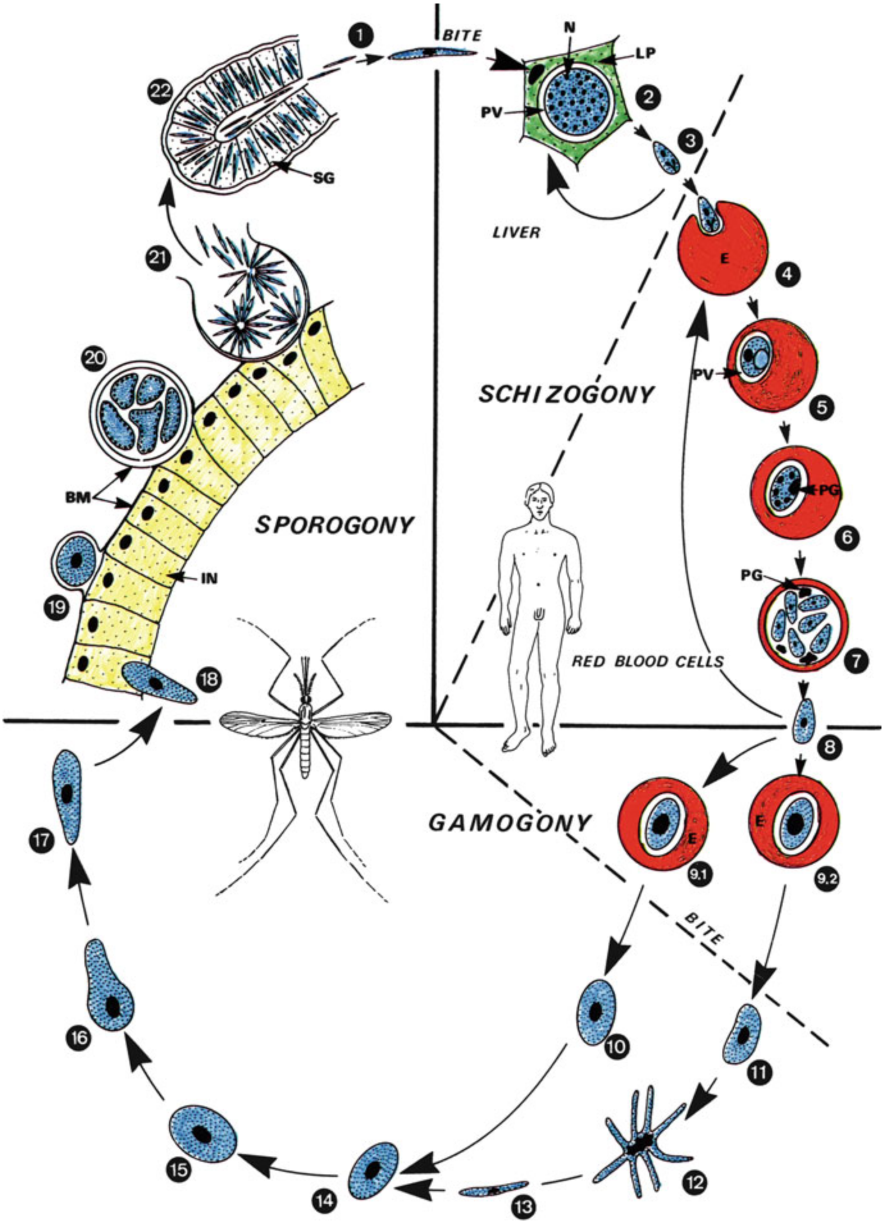

1
BITE
N
LP
22
PV
2
3
SG
LIVER
21
E
4
20
PV
5
SCHIZOGONY
PG
6
BM
SPOROGONY
IN
PG
19
7
RED BLOOD CELLS
18
8
17
GAMOGONY
E
E
9.1
9.2
BITE
16
10
11
15
12
14
13

Fig. 3.42 Life cycle of human malaria parasites (*Plasmodium* spp.) without reference to species-specific variations. (**1**) Elongate sporozoites are injected during bite of the female mosquito (*Anopheles* spp.). The sporozoites are distributed by bloodstream and enter liver cells lately within 2 min after infection. (**2**, **3**) Formation of schizonts and merozoites in liver parenchymal cells (exoerythrocytic phase). In some species this cycle may be preserved intracellularly via *hypnozoites* (**dormozoites**) for a long time (years) and cause relapses. (**4–8**) **Erythrocytic cycle**; liver merozoites enter (after typical prepatent periods) erythrocytes, grow to "signet ring stages" (**5**) and finally form, as schizonts (**6**), several merozoites (**7**, **8**). During the digestion of haemoglobin, the parasites produce pigment granules (**6**, **7**; PG) of haemozoin. The development

Later the trophozoites grow up to so-called schizonts, which produce depending on the species 8–32 merozoites. These are set free as soon as the erythrocyte bursts. Besides the merozoites also remnants of the red blood cells, the so-called pigment, is released, which initiates fever. The merozoites enter intact erythrocytes and repeat there the multiplication process inside a parasitophorous vacuole. This repeated asexual multiplication is called **schizogony**. Due to host influences, the schizogony process becomes synchronized leading to a rhythmic release of merozoites and the digested remnants of haemoglobin (pigment) (Fig. 3.45). The rhythm of cell disruption is characteristic for the different *Plasmodium* species. Thus the derived typical fever rhythms mainly depend on the simultaneous release of the merozoites and are less depending on the pigment, which appears brown blackish in the light microscope and is stored in the endothelium of blood vessels of several organs such as the brain, liver and kidney. It is considered as a marker for a persisting infection (Fig. 3.46).

In order to get the correct diagnosis of a malaria infection as early as possible, some facts have to be considered:

1. The typical fever in a species-specific characteristic rhythm does not occur during the early phase of an infection.
2. The synchronization of the rupture of the erythrocytes and the release of merozoites takes always a few days up to 1 week. In the meantime the fever shows no specific periodicity. This so-called Schüffner's initial fever persists as a continuum.
3. The typical enlargement of the spleen starts only at the end of the first week of infection.
4. Headache, muscle pain or variations of the rather low leucocyte levels may easily lead to the wrong diagnosis of a persisting malaria. In the case of **malaria tropica**, this misunderstanding might be fatal!
5. **Continua** are fevers which are stable within a range of only 1 °C for 24 h.
6. **Remitting fevers** stay high but vary mostly more than 1.5 °C within 24 h.

Fig. 3.42 (continued) of such schizonts becomes synchronous and is repeated (**4–8**) in a 1–3 day cycle (depending on the species). (**9**) After an indeterminate number of such asexual generations, some merozoites enter erythrocytes and become macro- (**9.1**) or microgamonts (**9.2**). The size and shape are species specific (banana shaped in *P. falciparum*). (**10–11**) When mosquito bites, they ingest erythrocytes containing such gamonts, which are released inside the gut from their enclosing erythrocytes. (**12**, **13**) The microgamonts develop four to eight microgametes within 10–15 min. (**14**) Fertilization of the macrogamete. (**15–19**) The resultant zygote quickly elongates and becomes a motile ookinete (**17**) which penetrates the peritrophic membrane in the mosquito's gut, migrates through the cytoplasm of a gut cell and begins its transformation into an oocyst (situated between the basal membrane and epithelial cells (**19**) (**20–22**)). Formation of multinucleate sporoblasts (**20**) which give rise to thousands of sporozoites (after 10–14 days). The latter become liberated into the haemocoel (body cavity) and migrate to salivary glands. These slender sporozoites (10–15 × 1 μm), which form a protecting surface coat, are finally injected into a new host at the next feeding act. *BM* basal membrane of intestine; *E* erythrocyte; *IN* intestinal cell; *LP* liver parenchymal cell; *N* nucleus; *PG* pigment; *PV* parasitophorous vacuole; *SG* salivary gland

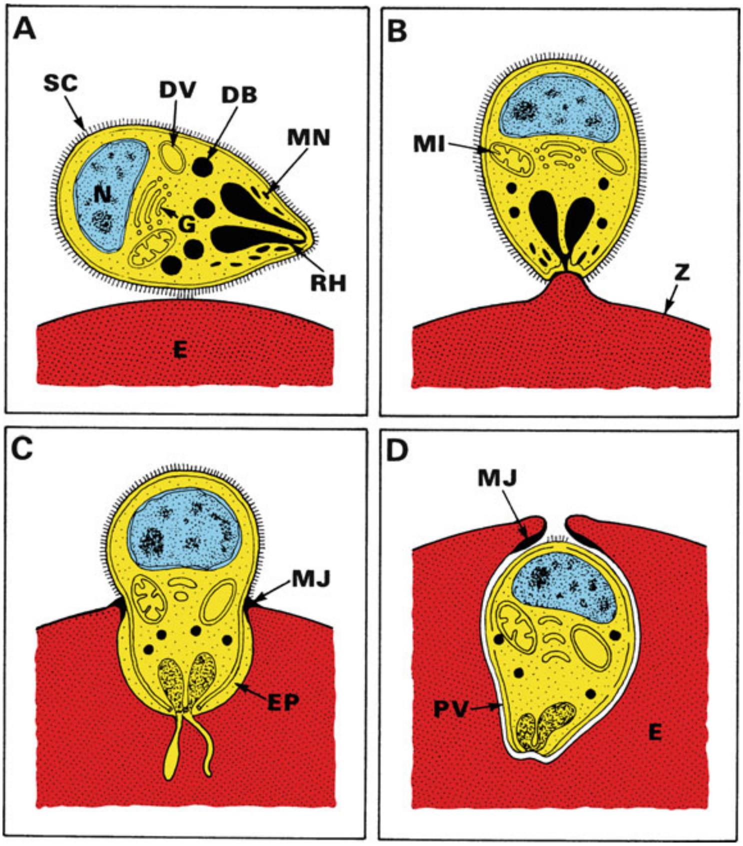
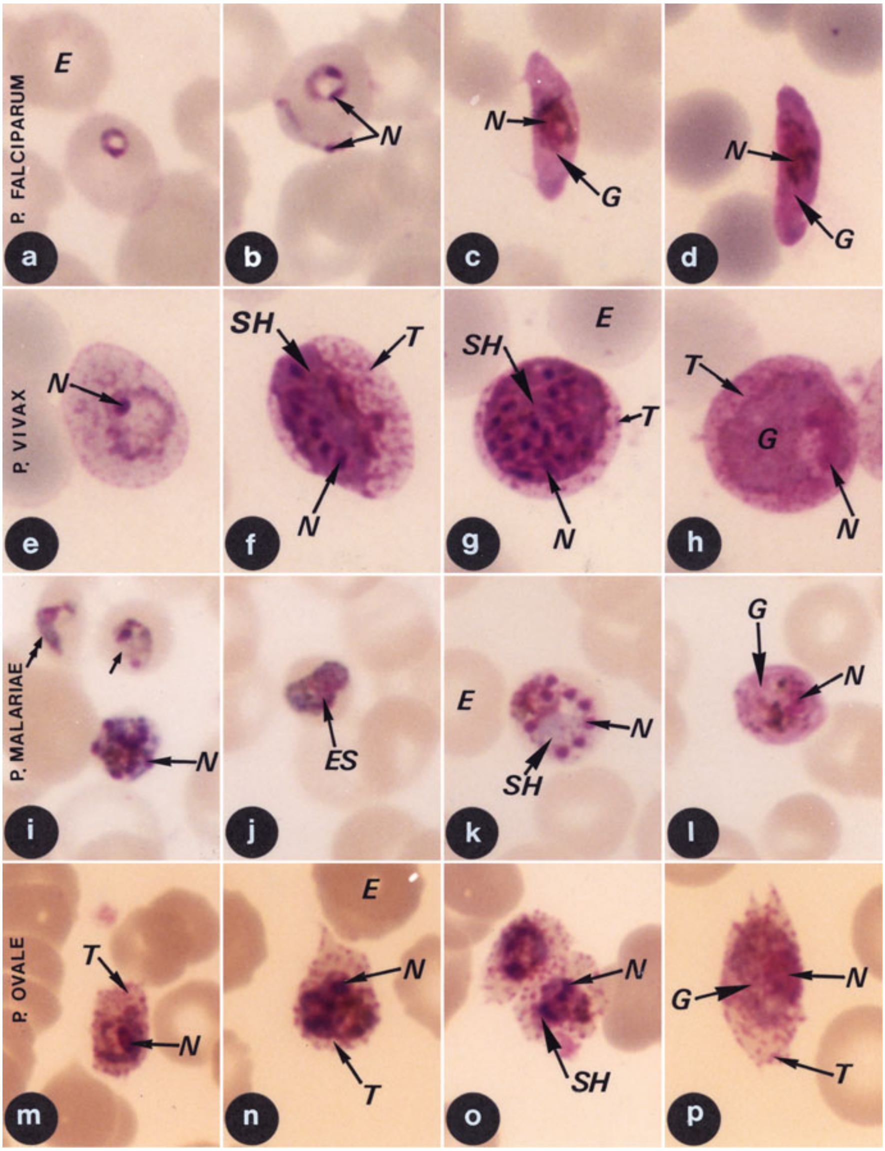


Fig. 3.43 Diagrammatic representation of the penetration of a merozoite of *P. falciparum* into an erythrocyte (note the occurrence of a moving junction (MJ). *DB* dense bodies; *DV* double-walled vesicle apicoplast contains the third genome; *E* erythrocyte; *EP* developing vacuole; *G* Golgi apparatus; *MI* mitochondrion; *MJ* moving junction; *MN* micronemes; *N* nucleus; *PV* parasitophorous vacuole; *RH* rhoptries; *SC* surface coat on the pellicle of merozoites; *Z* cell membrane

7. The case of periodically repeated phases without fever (=**intermittent fever**) is followed by differently high fever phases within 24 h (Fig. 3.47).

Five species of the genus *Plasmodium* may induce human in endemic areas/regions. They can be diagnosed with the help of their blood stages (Fig. 3.44) as well as by induced clinical symptoms:

(1) ***Plasmodium vivax***: agent of **Malaria tertiana**
(2) ***P. ovale***: agent of **Malaria tertiana**
(3) ***P. malariae***: agent of **Malaria quartana**
(4) ***P. falciparum***: agent of **Malaria tropica**


P. FALCIPARUM
P. VIVAX
P. MALARIAE
P. OVALE
a
E
b
N
c
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G
d
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e
N
f
SH
T
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Fig. 3.44 Light micrographs of the stages of the four most important human *Plasmodium* species: (**a**–**d**) *P. falciparum*; (**e**–**h**) *P. vivax*; (**i**–**l**) *P. malariae*; (**m**–**p**) *P. ovale*. *E* erythrocyte; *ES* schizont in development; *G* gamont; *N* nucleus; *SH* schizont; *T* Schüffner's dots

(5) ***P. knowlesi***: agent of a peculiar **Malaria tertiana**, which mainly occurs in monkeys, but actually is found increasingly in humans in South Asia

The determination of the exact *Plasmodium* species in smear preparation is vividly important for the success of a chemotherapy. Furthermore double infections with two species have to be considered, too. In this case the fever

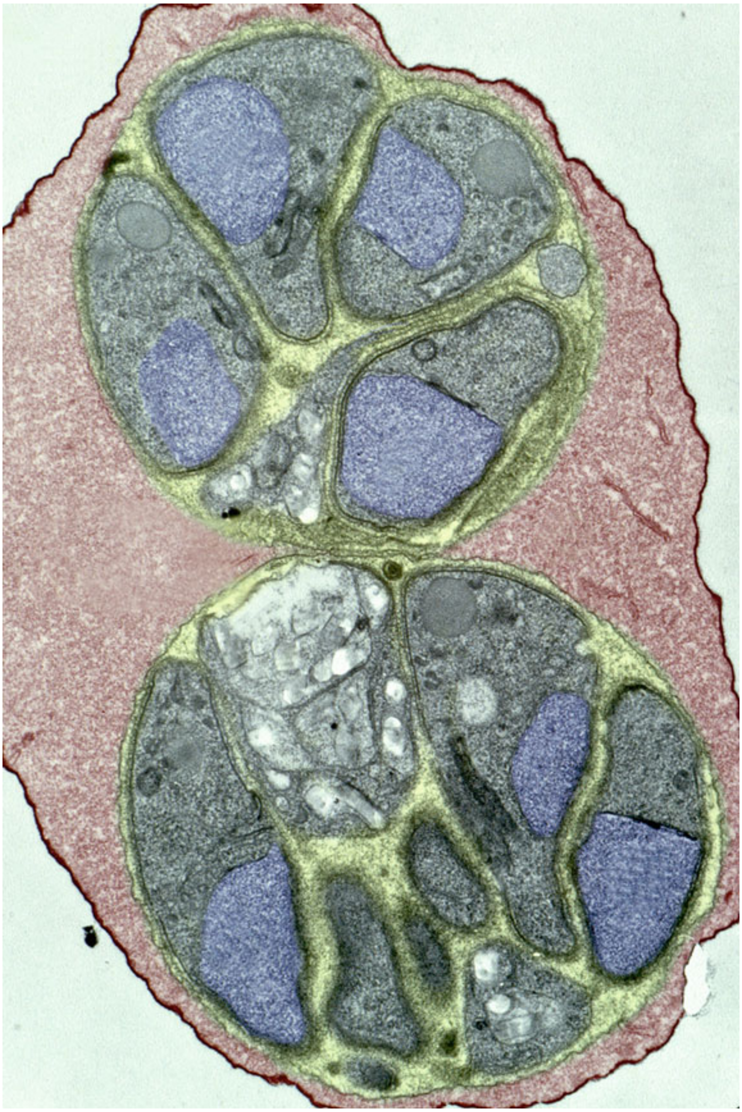

Fig. 3.45 Transmission electron micrograph of two schizonts of *Plasmodium falciparum* each within a parasitophorous vacuole inside an erythrocyte, which after rupture releases the crystalline pigment

attacks may overlap each other and thus indicate a continua fever, which in reality does not exist in this case. Smear preparations of *P. vivax*, *P. ovale* and *P. malariae* can be investigated at any time after the observation of clinical symptoms. However, in the case of *P. falciparum*, the blood must be investigated immediately and repeatedly, since many infected red blood cells are retained at the wall of blood vessels.

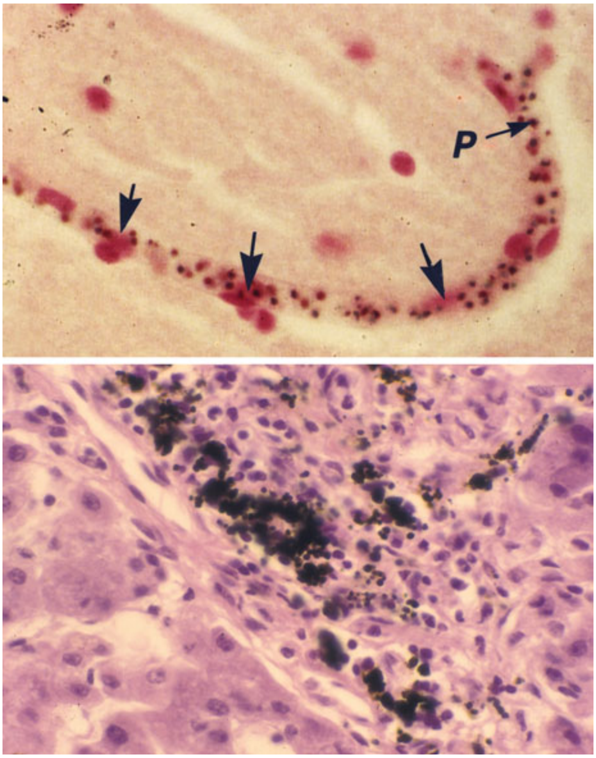

Fig. 3.46 Light micrograph of sections through blood vessels blocked either by erythrocytes containing pigment (*arrows upper figure*) or by blackish appearing pigment from disrupted erythrocytes (*lower figure*)

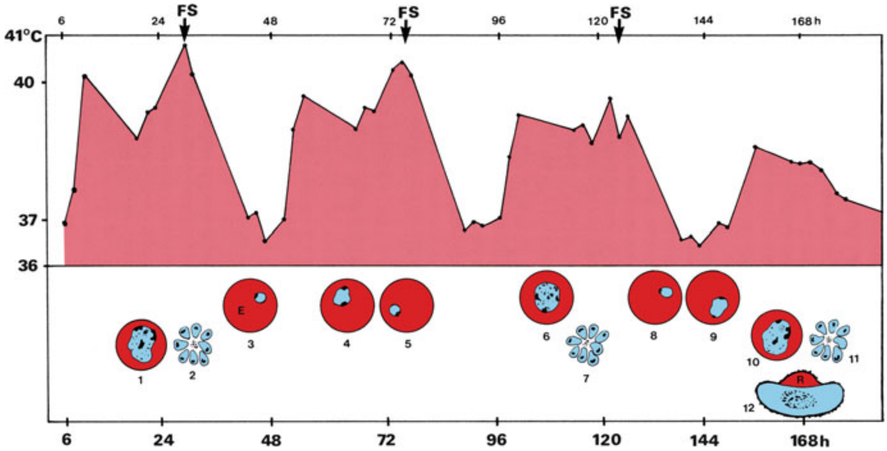

Fig. 3.47 Diagrammatic representation of the fever curve and development of the blood stages of *P. falciparum* in an infected human during four consecutive phases. *C* Celsius grades of fever; *FS* high fever phase; *h* hours

After repeated schizogonies in the blood, some merozoites are transformed to sexual stages (so-called gamonts), which stay in the blood for several weeks (=for the lifetime of the infested erythrocyte). In the case when a female *Anopheles* mosquito has been taken up such sexual blood stages, they grow in its intestine either to a single female macrogamete or to a microgamont forming many male microgametes. After fusion of the gametes to a zygote, a motile ookinete develops from the zygote. This ookinete penetrates the peritrophic membrane inside the intestine of the vector. Then it settles down in the space between the intestinal mucosa and the basal lamina and grows up there into an oocyst. This oocyst then gives rise to thousands of filament-like appearing sporozoites via an asexual reproduction (**sporogony**). These sporozoites migrate into the body cavity of the mosquito and later into the salivary glands, from where they are injected by the mosquito into the human host while sucking. The whole development process inside the mosquito takes place within 8–25 days depending on the outside temperature. The sporozoites, having entered the cells of the salivary glands of the mosquito, develop a surface coat, which protects them from the attack of the immune system of the human host. As soon as they are transmitted to humans, they enter within a few seconds to 2 min into the cells of the RES of humans (Fig. 3.42).

In the case of *P. vivax* and *P. ovale*, sporozoites can survive for several months or even years in the cells of the liver as hypnozoites or dormozoites before multiplying and leading to **recidives** (=starting new fever phases).

New malaria phases (relapses) based on hypnozoites are results of the reappearance of parasites in a formerly parasite-free blood. Such relapses are most common in the case of *P. vivax* infections. They occur – depending on the strain – up to 24 months after the end of the primary attack (which had lasted 7–28 days). An **exception in temperate regions** is made by the *P. vivax hibernans* strain. Here occurs the primary blood attack only after 8–12 months.

Recrudescence describes the reappearance of clinical symptoms in such cases, where a small number of infected erythrocytes occurred, which, however, was not sufficient to introduce significant heavy symptoms. In the case of *P. malariae*, the often reoccurring fever attacks (especially in the case of humans not staying in malaria areas for years) are results of this recrudescence phenomenon.

In the case of human malaria, no significant mammalian reservoir hosts occur, except for the *P. knowlesi*, where monkeys are the main hosts. Therefore infected humans are the reservoir, from where the vector mosquitoes obtain their infectious load.

In endemic regions humans develop a **semi-immunity** after repeated infections. Thus they mostly show only weak symptoms of the disease. Malaria hits, however, most severely young children leading to a high number of death cases. Some peculiar (sometimes also hereditary) diseases may protect children from severe malaria such as sickle cell anaemia (HbS), thalassemia or glucose-G-phosphate dehydrogenase deficiency. In these cases the parasites either cannot penetrate the erythrocytes or they cannot grow therein in a sufficient manner.

4. **Symptoms of the disease**
   (1) ***Plasmodium vivax* (Malaria tertiana)**

   Fever occurs after an incubation period of 9–18 days (sometimes it takes longer). The fever at first runs unspecifically, and only after the synchronization, the typical repeated fevers manifest (Fig. 3.5). Shivers occur (lasting about 1 h) every 48 h or may be seen in cases of two populations (strains) of parasites in a host also every 24 h. The fever reaches a height of about 40–41 °C and lasts several hours until finally the attack ends with a profuse 2–3 h lasting sweating. Without treatment 10–15 periods of such attacks may occur, slowly decreasing in their intensity. Recidives may occur as well for 5–7 years, mostly covering one or two phases of fever. If fever phases occur at intervals of 24 h, the disease is described as **malaria duplicate**.

   (2) ***Plasmodium ovale* (Malaria tertiana)**

   Fever occurs at intervals of 48 h (as it is the case in *P. vivax*) after an incubation time of 10–17 days. The symptoms of the disease disappear after 4–8 fever phases, but there may occur for up to 2 years.

   (3) ***Plasmodium malariae* (Malaria quartana)**

   Fever may occur after an incubation time of up to 6 weeks (this is important to know for returned travellers). After synchronization and shivers, high fever phases (40–41 °C) occur at intervals of 72 h. If different populations of the parasites are involved, fever may occur every 24 or 48 h, being repeated up to 20 times in non-treated cases. Recrudescences may also occur after extremely long periods (up to 30 years) have been documented.

   (4) ***Plasmodium falciparum* (Malaria tropica)**

   The incubation period is about 14 days (8–24 days). Thus an infection might be manifested at home just after an 8 days staying in an endemic region, if prophylactic chemotherapy did not work or was not done. On the other hand, severe delays may occur in the individual fight against the disease in the case of an insufficient prophylaxis or due to drug resistance of the strain of the parasite. This may result in the fact that attacks of **malaria tropica** possibly occur even weeks and months after leaving the endemic region! The fevers due to *P. falciparum* occur irregularly and reach 39–40 °C. Sometimes a so-called continua fever may occur which is constantly high. In rare cases the malaria tropica shows only mild fever or even no fever (**algid malaria**; Latin: *algidus* = cold). **Malaria tropica** is the type of malaria where the range of the fever phases is most irregular. **Accompanying symptoms** are fatigue, headache and an increasing feeling of illness.

   Laboratory tests show normal or somewhat lower numbers of leucocytes, a decrease of thrombocytes, a progressive erythrocyte sedimentation reaction and an increasing anaemia. The life-threatening progress of

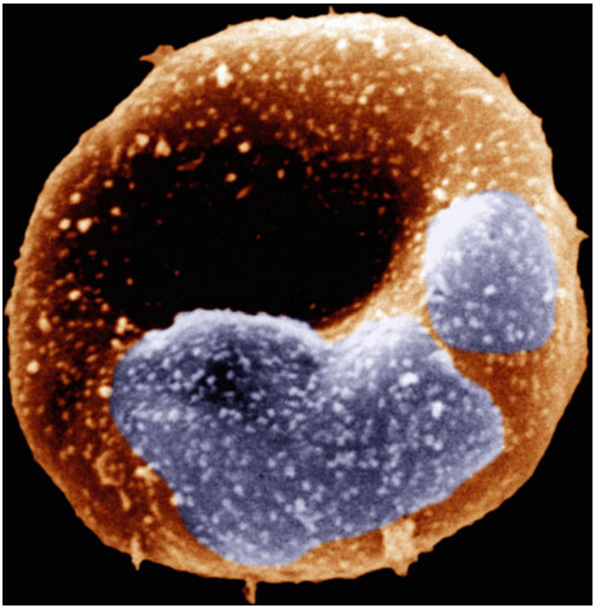

Fig. 3.48 Scanning electron micrograph containing two schizonts (stained in *blue*) of *Plasmodium falciparum*. Note that at the surface, so-called knobs (=*white dots*) appear as a follow-up of surface constrictions due to the invaded parasites (compare Fig. 3.49)

the disease in the case of the malaria tropica is opposite to the other malaria forms. Here erythrocytes which contain parasites become attached to the capillary walls, because these erythrocytes develop peculiar surface protrusions called **knobs** to stick at the capillary surface (Figs. 3.48, 3.49). This blocks the microcirculation and leads to stasis, acidosis, perivascular oedema and to petechial bleedings. Depending on the different sites of organ infestation, severe and progressive organ lesions occur starting from the fourth to the fifth day of illness. When occurring in the brain, they are described as **cerebral malaria** leading to severe headache and loss of consciousness and brain oedema leading to cramps, seizures and further neurological malfunctions introducing coma. These cerebral symptoms are the most common reasons of death in the case of malaria tropica.

Severe lesions of organs may also include the kidneys leading to an acute **renal malaria**, which leads to failure of function and requires urgent dialysis. Also the lungs may be afflicted showing interstitial and alveolar oedema. Also the cardiovascular system may suffer severely from cardiac arrhythmia up to aneurismal dilation of the myocard. The liver damage may introduce a severe hepatical icterus as a sign of organ dysfunction. The intestine may produce intense diarrhoeas, which endanger the water balance of the body. **Black water fever** may occur due to a severe haemolysis due to kidney destruction based on increasing tubular necrosis.

The haemolysis is not sufficiently explained by the bursting of parasite-infected erythrocytes. The variety of the symptoms resulting from organ

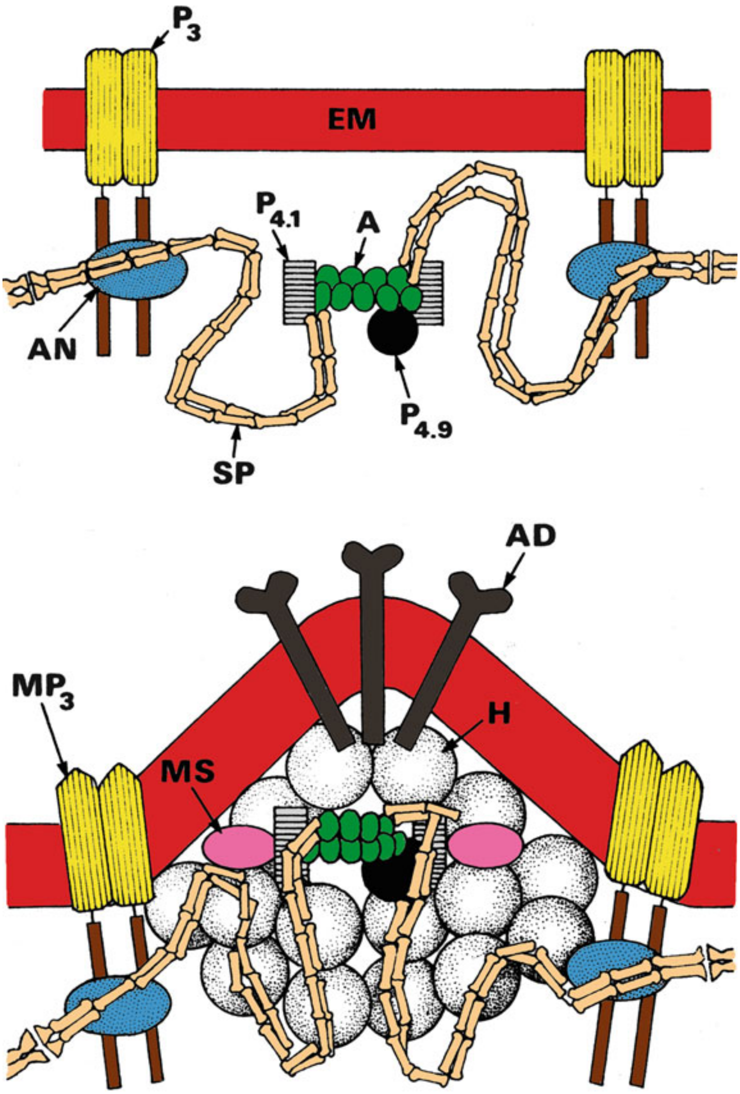

Fig. 3.49 Diagrammatic representation of the arrangement of the chemical components at the surface of an erythrocyte in an uninfected stage (above) and in case of an infection with *Plasmodium falciparum* stages after results of Foley and Tilley. At the surface of infected red blood cells, so-called knobs appear, which are formed by several components. These changes lead to the effect that the surface of the infected erythrocytes losses its flexibility. *A* actin; *AD* adhesion proteins (e.g. sequestrin); *AN* ankyrin; *EM* membrane of the erythrocyte; *H* HRP-1-protein (=knob protein); *MP*$_3$ modified protein-3; *MS* MESA (mature parasite erythrocyte surface antigen; *P*$_3$, *P*$_4$, *P*$_{4,9}$ proteins (bands); *SP* spectrin dimers

lesions unfortunately leads rather often to a fatal wrong diagnosis. Thus it is very important to diagnose malaria at a very early stage, what makes it possible to start quickly a successful treatment.

In Germany 1500–2500 cases of malaria are counted year by year. 70 % of them show Malaria tropica. 90 % of these cases were introduced to Germany from Africa. 4 % of these cases in the last 10 years had been lethal. Adverse factors hereby had been none or insufficient prophylaxis, respectively, a wrong diagnosis (e.g. flu, hepatitis, encephalitis, pyelonephritis, feverish diarrhoea). In cases when patients are older than 60 years, the disease has been lethal for 16 % of the diseased persons. Especially children below 12 years are highly endangered.

Over 200 million humans are afflicted by malaria and up to 1.0 million people die each year.

5. **Diagnosis**: The proof of the parasitic stages in the blood is the most important! They can be shown in **blood smears**, but the **thick droplet method** is especially useful to discover parasites in cases of a low parasitemia (<0.1 %), because this method leads to an enrichment ratio of 20 times up to 40 times. However, it is difficult to diagnose the different species with the help of light microscopy; frequently only the differentiation between *P. falciparum* and non-*falciparum* species is successful. For the diagnosis of the different species, the following criteria are important (listed in Tables 3.6, 3.7, 3.8, 3.9 and 3.10 and in Fig. 3.44). The different methods used in light microscopy are described on Plates 3.1–3.3.

Detailed Diagnosis (Fig. 3.44)

(1) ***Plasmodium falciparum***

(a) Normally only single-nucleated trophozoites in the ring stage occur in smear preparations. These stages are mostly very tiny (reaching only 1/3 of the diameter of the erythrocyte). Sometimes they contain two nuclei, which may be situated side by side or opposite to each other (Fig. 3.44). In the case of a high parasitaemia, two or more ring forms are observed in a single erythrocyte. Besides these common stages, trophozoites other than ring-shaped ones occur. They are situated close to the inner membrane of the red blood cell and are so-called accolé forms.

(b) Schizonts containing 8–24 (or up to 32) merozoites are rarely found in the peripheral blood. A peripheral schizontemia occurs mostly only in cases of severe infections and is a sign of a severe infection with a bad prognosis.

(c) The infected erythrocytes have a normal size and are only slightly stained; they are not deformed and do not show fleckings. Only erythrocytes containing old trophozoites or schizonts sometimes may show bluish fleckings (**Maurer's dots**).

Table 3.6 Comparison of the developmental cycles of the *Plasmodium* species of humans

Species	Prepatent period = interval between infection and the first ability to detect the parasite	Mean of beginning of erythrocytic schizogony	Duration of erythrocytic schizogony	First appearance of gamonts in blood
P. vivax	8 d	13–17 d	48 j	11–13 d
P. ovale	8 d	13–17 d	48 h	20–22 d
P. falciparum	5 d	8–12 d	36–48 h	17–22 d
P. malariae	13–17 d	28–37 d	72 h	24–31 d

d days; *h* hours

Table 3.7 Characteristics of the asexual blood stages of *Plasmodium* species of humans

Species	Parasite stages in peripheral blood	Size of trophozoites	Number of schizont nuclei	Pigment	Changes of host cells
P. vivax	All	2/3 RBC	12–24	Yellow brownish	Strongly enlarged with Schüffner's dots
P. ovale	All	2/3 RBC	6–12	Light brown	Slightly enlarged, scraggy, surface, Schüffner's dots
P. falciparum	Mostly signet ring stages (trophozoites), gamonts	1/5 RBC	8–24	Scattered: light brown; as lumps dark brown	Mostly none, occasionally Maurer's dots
P. malariae	All	2/5 RBC	6–12 (eight often arranged like a rosette)	Dark brown	None most of the time

RBC red blood cell

(d) The big banana-shaped gamonts are characteristic for *P. falciparum*. They first occur inside the blood during the earliest 7 days after the first fever attacks. There they stay for months (also after a therapy). This is why they also can be found in apparently healthy persons in endemic regions and can infect for long mosquitoes.

(e) In contrast to other *Plasmodium* species, the erythrocytes infected by *P. falciparum* become attached to the capillary walls of the liver, spleen and other organs only shortly after the merozoites had entered

Table 3.8 Characteristics of sexual blood stages of *Plasmodium* species of humans (Giemsa stained)

Species	Form	Microgamont	Macrogamont
P. vivax	Spherical/ ovoid	10 µm, nucleus red, cytoplasm pale blue/pink; pigment fine grained	11 µm; nucleus small, dark red; cytoplasm blue, plenty of pigment
P. ovale	Spherical/ ovoid	9 µm, similar to *P. vivax*	9 µm, similar to *P. vivax*
P. falciparum	Sickle or banana shaped	9–11 µm, nucleus big and diffuse; cytoplasm pink; pigment diffusely dispersed	12–14 µm; central nucleus, red; cytoplasm blue to purple; pigment concentrated around the nucleus
P. malariae	Spherical/ ovoid	7 µm, like *P. vivax*	7 µm, like *P. vivax*

Table 3.9 Comparison of the clinical symptoms of the different human malaria types

Criterion	*P. falciparum*	*P. vivax*	*P. ovale*	*P. malariae*
Average incubation period	8–24 days	9–18 days	10–17 days	18–40 days
Prodromal symptoms	Influenza-like	Influenza-like	Influenza-like	Influenza-like
Fever	Daily, recurrent or continuing	Sporadic to daily	Sporadic to daily	Periodically every 72 h
Periodicity of established fever attack	No fever; permanent fever or every 36–48 h	48 h	48 h	72 h
Initial paroxysm	Severe, for 16–36 h	Slight to severe, for 10 h	Slight for 10 h	Slight to severe, for 11 h
Duration of untreated disease	2–3 weeks	3–8 weeks or even longer	2–3 weeks	3–24 weeks
Duration of persistence of parasites in an untreated disease	6–8 months	5–7 years	Up to 2 years	30 years or more
Anaemia	++++	++	+	++
CNS syndrome	++++	+/–	+/–	+/–
Kidney syndrome	+++	+/–	–	+++
Blackwater fever	++++	+	+	+

+, present, frequency; –, absent

them. That is why only young ring stages can be observed in a blood smear preparations and thus they can be missed in the case of few tests. Therefore repeated probings are very important (also at the end of the fever attacks). Otherwise it is possible to miss or to delay the diagnosis fatally.

Table 3.10 Malaria prophylaxis (according to the German Society of Tropical Medicine and International Health)

Product	Prophylaxis start	Prophylaxis end	others
Atovaquone/ Proguanil (Malarone®)	1–2 before entry into malaria region	7 days after leaving malaria region	Some restrictions
Chloroquine (Resochin®, Weimerquin®, Quensyl®)	With entry of malaria regions without chloroquine resistance	6 weeks after leaving malaria region	Prophylactic dose: 300 mg base per week
Chloroquine plus Proguanil (Paludrine®)	See Proguanil	See Proguanil	
Doxycycline			In Germany not approved for prophylaxis
Mefloquine (Lariam®)	2 weeks before start of travel to regions without mefloquine resistance	2–3 weeks after return	Caution: mental side effects are possible

(2) ***Plasmodium vivax***

(a) Depending on the stage of the schizogony in the erythrocytes, different forms of the parasites can be observed: **ring stages** with one nucleus and **growing** or **mature schizonts** with 12–24 merozoites. The ring stages are **normally** bigger than those of *P. falciparum* (reaching about 2/5 of the erythrocyte). Single ring stages with two nuclei, single accolé stages and several stages are, however, only rarely observed. Very often the parasites show in all erythrocytes the same stage of development. Sometimes, however, several or all stages can be seen at the same time.

(b) The infected erythrocytes (reticulocytes) appear enlarged and hypochromic, are sometimes slightly deformed and show small eosinophilic granula in their interior (the so-called Schüffner's dots). These peculiarities may be absent in the case of very young ring stages of the parasite.

(c) Male and female gamonts can be seen already 3 days after the start of the blood schizogony with their nucleus lying in the middle (male) or marginally (female) of the cell.

(3) ***Plasmodium ovale***

The blood stages are very similar to those of *P. vivax*. The infected erythrocytes are mostly not or very slightly enlarged. Their shape is ovoid or polymorphic and may show protuberances along their limiting membrane. They contain Schüffner's dots, but these are coarse and strongly coloured. The schizonts produce mostly 8–10 merozoites and only rarely up to 16. The gamonts are smaller than the erythrocytes.

(4) ***Plasmodium malariae***

The growing schizonts of this species may appear as a band. The mature schizonts develop only eight (6–12) merozoites, which are often arranged in a ring around the central pigment appearing like a daisy flower. The gamonts remain relatively tiny. The infected erythrocytes are not enlarged neither deformed and do not show Schüffner's dots. Double infections, especially together with *P. vivax* or *P. falciparum*, may occur. Rarely also triple infections are seen. This phenomenon has to be considered when selecting the means of therapy, because of the needed different therapies. If the blood smear and the thick droplet tests are negative, the probings must be repeated for at least 2–3 days to exclude malaria properly. Other tests to diagnose *Plasmodium* stages are also existing, i.e. fluorescence microscopy or QBC = quantitative buffy coat analysis. Furthermore circulating antigens can be observed by PCR and varieties of DNA in situ hybridization. These new methods are very important tools for research and epidemiologic investigations. But in no way they can substitute the proof of the parasites in the blood by examining thick droplet preparations or blood smears, because these methods offer quick results, are cheap and are available everywhere. Compared to molecular biological methods, the classic methods show a high sensitivity and the unreachable specificity of the gold standard. When lethal cases of humans occurred in Europe, this was nearly exclusively due to the fact that these simple blood tests were not done or were not carried out properly.

6. **Pathway of infection**: Percutaneously by the bite of nightly active female mosquitos of the genus *Anopheles*. **Caution**: The transmission by blood transfusion is possible, since schizonts survive at low temperatures (although they stop dividing) in a fridge.

   Attention: Malaria parasites also stay alive in the intestine of leeches for a long time.
7. **Prophylaxis**:

   (1) **General advices to avoid infections**
   - Repelling of mosquitoes by special products, which are sprayed onto the skin and clothes (e.g. Autan®, Viticks®)
   - The use of mosquito nets over beds in the tropics
   - The use of mosquito gaze at windows and doors
   - Spraying of insecticides (pyrethrum derivates) in sleeping rooms and on mosquito nets

   (2) **Chemoprophylaxis**

   A chemoprophylaxis is generally recommended in the case of travelling to malaria-afflicted countries. In this way the risk of being infected can be reduced – also in regions where resistant *Plasmodium* strains occur.

   The decision on the individual mode of prophylaxis has to be made depending on the place, time in the year and on the travelling mode. Other factors are the age of travellers, a possible pregnancy, previous illness, intolerance of medication or ongoing use of possibly interfering medications. In the case of an ineffective prophylaxis in regions, where drug resistance of parasites occurs, it is recommended to bring along therapeutic doses of a reserve medication. If symptoms are shown and the next physician is in far distance, the reserve may be used as an emergency treatment. If the staying in endemic regions is only short, no prophylaxis might be needed. Nevertheless it is strongly recommended to consider potential malaria symptoms after returning home. This management should be restricted for travels into regions with a low risk of malaria and in cases where intolerance to medication exists. **Caution**: Irregular medication, vomiting or diarrhoeas lead to ineffectiveness of prophylaxis medications.

Vaccination: Different vaccines are under development or testing but none is really available to offer a full protection for travellers.

8. **Incubation period**

P. falciparum: 8–24 days
P. vivax: 12–18 days
P. ovale: 10–17 days
P. malariae: 18–42 days

9. **Prepatent period**

The minimal period of time for the exoerythrocytic schizogony in the liver (=appearance of the first stage in the blood) are:

P. falciparum: 5 days (average 8–12)
P. vivax: 8 days (average 13–17)
P. ovale: 8 days (average 13–17)
P. malariae: 13–17 days (average 18–37)

10. **Patency**

P. falciparum: under treatment 4–6 weeks, without treatment max. 18 months
P. vivax: 5–7 years
P. ovale: up to 2 years
P. malariae: 30 years and more
P. knowlesi: not yet completely defined

11. **Therapy**: Chloroquine (Resochin® and others) is the drug of choice to be used in the case of malaria tertiana and malaria quartana (however, resistances of *P. vivax* have been observed). The WHO standard treating scheme is as follows: initial application of 600 mg chloroquine base (children 10 mg/kg bodyweight). This dose is comparable to four tablets of Resochin® 250 mg (1000 mg chloroquindiphosphat) given. After 6 h at the second and third days, the patient has to be repeatedly treated with 300 mg base (children 5 mg/kg

bodyweight) (Fig. 3.51). In the case of malaria tertiana, a treatment must be followed to prevent relapses: primaquine 15 mg (children 0.25 mg/kg bodyweight) daily for 2 weeks. **Caution**: Danger of hemolysis exists in the case of glucose-6-phosphate-dehydrogenasis deficiency.

The therapy of the malaria tropica, which should preferably be done in a hospital, depends on:

- The severity of the illness
- The resistance situation in the region of the infection (R-I and R-III resistances)
- Previously ingested drugs for chemoprophylaxis
- The product used in a previous treatment scheme

Each year the German Tropical Medicine Society and other international institutions compile results and give a detailed overview of the situation where drugs are suitable for the chemotherapy – depending on the region and potential resistances.

Important: It is highly recommended to discuss the dosage of the drugs with the physician (considering the patient's age, weight and possibly preexisting conditions).

The uncomplicated malaria should be treated (as the WHO recommends) by a combination based on artemisinin (artemether/lumefantrine) such as Riamet™ or Coartem™.

Treatment Dosages[1]

1. **Riamet™ (artemether/lumefantrine)**: 80/480 mg (=4 pills) initially, after 8 h four further pills. Then four pills 2× daily on days 2 and 3 (=a total of 24 pills) starting at a body weight of 35 kg.
2. **Malarone® and generica (atovaquone/proguanil)**: 1000 mg/400 mg (=4 pills) as single dose on 3 following days starting at 40 kg bodyweight.
3. **Lariam® (mefloquine)**: Initially 750 mg (3 pills), after 6–8 h further 500 mg (=2 pills); if the body weight exceeds 60 kg, another 250 mg (=1 pill) has to be given.
4. **Eurartesim® (piperaquine tetraphosphate + dihydroartemisinin)**: 120 mg/960 mg (=3 pills) as a single dose on three consecutive days starting in the case of persons of 36–75 kg bodyweight. In the case of a bodyweight of more than 75 kg, four pills should be given for 3 days (controlled application by medical doctors).
5. **Resochin®, Quensyl® (chloroquine)**: Only in limited regions, 600 mg base (=4 pills), then 6, 24 and 48 h after the start of the medication always 300 mg.

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[1] **Recommendations** according to the German Society of Tropical Medicine (2015).

Caution: Before any treatment check the recent "state of the art", since recommended dosages/products may have changed.

A **complicated malaria** has to be treated right from the start and needs a clinical intensive care:

(1) The therapy starts with a loading dosage of chinine: iv 20 mg chinine/kg bodyweight for the first 4 h.
(2) Then 10 mg chininehydrochloride/kg bodyweight has to be given 3× daily for 7–10 days by infusion.

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The discovery of chinine	
1600:	Discovery of the bitter substance in bark of a tree called “China bark tree” in the mountains of South America. (Indian: good bark; scientific name of the genus: *Cinchona*)
1633:	First reports of successful treatment of malaria in South America, Peru and Ecuador. The disease was distributed to South America by Africans who came as slaves to South America. Chinine was introduced to Europe as so-called Jesuit’s powder or as “lady’s powder” (after the legend that the wife of the governor of Peru was the first white person cured from malaria)

(continued)

The discovery of chinine	
1700:	Overexploitation of those trees in South America to sell the bark. Culturing those trees in Indonesia leads to the monopole of chinine production for the Dutch East Asia Company
1820:	Pelletier and Caventou, two young French chemists, discover the chemical structure of the alkaloid chinine
1867:	The German Binz proves that the malaria parasites are destroyed by chinine
1880:	Germany imports 28,000 kg of the so-called China bark per year
1929:	The German scientist Rabe (Bayer Company) synthesizes chinine chemically. Too many treatments and the use of too low dosages led to an increasing resistance of the malaria parasites against chinine worldwide. Chinine is not always used as antimalarial drug
1998:	The clinical chinine-resistant strains of *Plasmodium* species have mostly disappeared. Chinine is used again as an emergency drug to rescue patients from symptoms of several types of malaria

Plate 3.1: Smear Preparation

A little drop of blood is placed onto a glass slide, spread there to form a thin layer (Fig. 3.50) and dried at air. Thereafter the following procedures are done:

1. Fixation of the dry smear preparation by methanol for 3 min.
2. Drying of the smear preparation at the air.
3. Colouration according to Giemsa for 30 min.
4. Discharging the colouration compound with the help of water.
5. Covering the dry smear preparation with Eukitt or relevant material.
6. Investigation of the coloured preparation with the help of a light microscope (40×, 100×).

Plate 3.2: Thick Droplet Method (in Cases of a Low-Grade Parasitaemia)

A droplet of blood (1–3) is placed onto a glass slide and stirred with the help of a needle or a glass slide (see Fig. 3.50 below) in order to avoid coagulation and to delete the fibrin. After air-drying, which can be accelerated with the help of the heat from a hairdryer, tap water is put on this slide until the red colour of the disrupted erythrocytes is washed out. After drying this slide, the so-called thick drop preparation becomes coloured with the help of Giemsa solution – however, previous fixation is omitted. Another colouration is that of Hansen which is done with the help of alum haematoxylin after previous ether-ethanol (1:1) fixation.

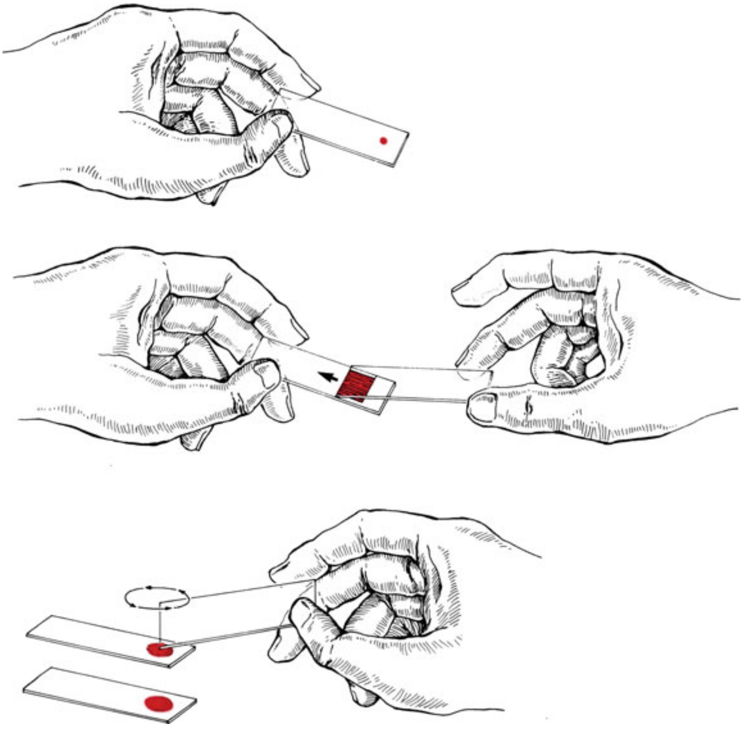

Fig. 3.50 Diagrammatic representation of the process to prepare a blood smear (above, middle) and a so-called thick droplet to demonstrate *Plasmodium* stages

Plate 3.3: Materials

1. 0.1 ml heparin (100 units/ml) for 5–10 ml blood.
2. 0.1 ml K_3 EDTA (0.38 M/ml) for 10 ml blood.
3. Citrate anticoagulants: 7.3 g citron acid, 22 g Na-citrate and 24.5 g glucose, added to 1 l aqua dest.

   15 ml of this anticoagulants is sufficient for 100 ml blood.
4. **Staining solution according to Giemsa**

   0.3 ml azur-eosin methylene blue solution (Merck No. 9204) to be added to 10 ml Weise buffer consisting pH 7.2: 0.49 g KH_2 PO_4 + 1.14 g Na_2 HPO_4 to be added to1 l aqua dest.
5. **Alaunhaematoxyline staining according to Hansen:**
   - A. 1 g haematoxylin in 10 ml absolute alcohol
   - B. 20 g Kalialaun diluted in 200 ml warm aqua bidest and filtered afterwards.
   - C. 1 g Kalialaun in 16 ml aqua bidest diluted.

(continued)

Plate 3.3 (continued)

After 1 day waiting time, solutions **A** and **B** are mixed, and during stirring, exactly 3 ml of solution **C** are added. The new solution (A + B + C) is heated (at 100 °C) for 1 min and afterwards cooled down and filtered.

6. **Eukitt embedding**

   One droplet of Eukitt is placed onto the glass slide containing the coloured smear preparation, is covered with a small thin cover glass and then pressed slightly down.

3.17 *Babesia* Species (Babesiasis, Babesiosis)

1. **Name**: The genus name honours the Romanian scientist Victor Babès (1854–1926), who first described these species.
2. **Geographic distribution/epidemiology**: Worldwide in regions with ticks; e.g. in the USA and in Europe, numerous cases of human babesiosis have been documented. Thus this disease should also occur in many other rural countries (but this is not detected yet) (Fig. 3.51).

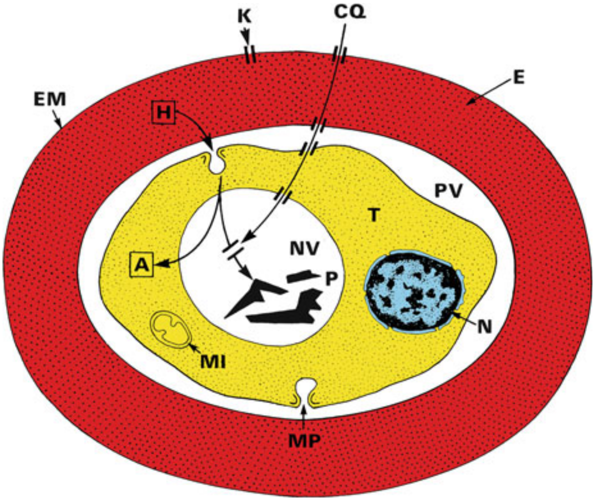

Fig. 3.51 Diagrammatic representation of the effects of chloroquine (CQ) on intraerythrocytic stages of *Plasmodium* species. CQ passes through several ionic channels (K) into the inner of the parasitophorous vacuole (PV) inside the parasitized erythrocyte. The CQ blocks the digestion of the haemoglobin (H), while the digested globin results in amino acids (A) which are transported into the cytoplasma. *A* amino acids; *E* erythrocyte; *EM* membrane of the erythrocyte; *MI* mitochondrion; *MP* micropore cytostome; *N* nucleus; *P* pigment = remnants of haem; *PV* parasitophorous vacuole

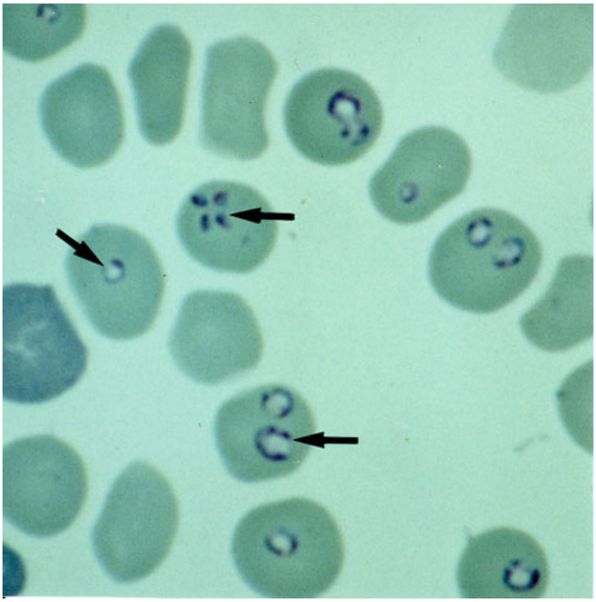

Fig. 3.52 Light micrograph of a Giemsa-stained blood smear preparation containing erythrocytes filled with different developmental stages of *Babesia microti* (*arrows*). Very typical are the so-called tetrads, giving rise to four new infectious stages

3. **Biology, morphology**: Stages (called sporozoites) of some *Babesia* species are transmitted via saliva from *Ixodes* ticks to humans, where red blood cells are penetrated and finally destroyed. The stages inside the erythrocytes reach (depending on the species) a length of 2–5 µm. They are situated immediately inside the cytoplasm of the red blood cell and start reproduction by binary fission (Fig. 3.52). This reproduction leads to the repeated destruction of infected red bloods cells. One to two weeks after the infection, some spherical parasitic stages are formed (representing gamonts = sexual stages), which after the uptake of another blood-sucking tick develop male and female gametes inside the intestine. After their fusion motile ookinetes are formed, which enter the salivary glands of the tick. The large numbers of 1–2 µm sized sporozoites are asexually produced which are transmitted during the next blood-sucking to another vertebrate host (=possibly also to humans). In humans the specimens of the following species have been diagnosed which are normally transmitted to animal hosts, but occasionally also to humans:
   (a) *Babesia divergens* (rodents, cattle), vector (*Ixodes ricinus*)
   (b) *Babesia microti* (rodents), vectors (*Ixodes ricinus*, *I. dammini*)
   (c) *Babesia canis* (dogs), vectors (species of the genera *Rhipicephalus, Haemaphysalis* (Fig. 5.10)
   (d) *Babesia bigemina* (cattle), vectors (*Boophilus* species)

The first two above-listed *Babesia* species develop rather small stages (2.5 μm) inside erythrocytes; the other two have big erythrocytic stages, which are larger than 3.0–3.5 μm.

4. **Symptoms of the disease (Babesiosis)**: In Europe first cases of babesiosis were described in the year 1956. Since then more than 100 documented cases were published by French groups already in the year 1991 (Gorenflot and Brasseur 1991). Most cases were very severe and ended about 50 % fatally. Considerably more cases were found by occasional serological investigations. Thus it can be supposed that there are many cases not detected, since the symptoms are not very specific. The **acute babesiosis**, which leads to lethal outcome in 50 % of the cases, was exclusively diagnosed in splenectomized persons, which were infected by *Babesia divergens*. The **chronic**, mostly **latent**, form of the disease was diagnosed in healthy (perhaps weak) persons and derived from infections with *Babesia microti*. The symptoms are rather nonspecific and may also be observed in initial cases of **malaria tropica**, so that misdiagnosis might occur. **Symptoms of babesiosis** start with headache, loss of appetite, diarrhoeas, vomiting, shivers and fevers of up to 40–41°C and also sweating, high pulse, pain in legs, arms of abdominal muscles and a haemolytic-anaemic blood picture. In cases of the **severe babesiosis**, these symptoms are increased in severity within a few hours – often accompanied by invasion of 50 % of the erythrocytes. As in malaria tropica, severe babesiosis introduces soon symptoms such as coma and reddish urine. Death occurs due to loss of the activity of the brain and the kidneys.
5. **Diagnosis**: For the interpretation of the early symptoms, it is very important to know whether the patient had contact to ticks or tropical mosquitoes within the last weeks before the occurrence of symptoms in order to exclude either babesiosis or malaria. Microscopic diagnosis of *Babesia* species stages is based on the appearance of pear-shaped stages in division or the occurrence of so-called Maltese cross stages (Fig. 3.52). The Giemsa stain is a recommended colouration. However, the grade of parasitaemia varies depending on the species (e.g. *B. divergens* reaches a parasitaemia up to 50 % and *B. microti* only about 1–2 %). The use of the so-called thick droplet technique is only needed in very low-grade infections. A very significant symptom of a babesiosis is the occurrence of a considerably high-grade haemolytic anaemia.

   For the differentiation of *Babesia* stages from those of *Plasmodium* species, the following criteria can be used:

   (1) *Babesia* merozoites are mostly pear shaped and are mostly seen in division.
   (2) *Babesia* do not form multinucleated schizonts (at maximum tetrads are formed).
   (3) Parasitic stages of *Babesia* never contain dark/black **pigment** (=similar to non-digested remnants of haemoglobin in *Plasmodium* species).
   (4) *Babesia* stages are always situated directly inside the cytoplasm of the erythrocyte and never in vacuoles, as are the *Plasmodium* stages. This

vacuole in the latter case can, however, only be seen with the help of electron microscopy.

6. **Pathway of infection**: Percutaneously during the blood-sucking act of ticks of the genus *Ixodes*. However, transmission of *Babesia* stages may also occur during blood transfusion.
7. **Prophylaxis**: The use of repellents (e.g. Viticks®, Autan®), which must be sprayed onto shoes, socks and clothes in order to avoid attacks of *Ixodes* ticks.
8. **Incubation period**: 1–4 weeks.
9. **Prepatent period**: 1 week.
10. **Patency**: 1 year (or longer?)
11. **Therapy**: There are many trials of treatment reported; however, none were fully and always effective. The following therapy schema of Gorenflot and Brasseur (1991) saved the life of many persons:
    (1) Application of fresh blood.
    (2) IV application of clindamycin (3–4 × 600 mg per day).
    (3) Additional application of chinine (3 × 600 mg per day).
    (4) These applications were done for 10–11 days.

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3.18 *Balantidium coli* (Balantidiasis)

1. **Name**: Greek – *balantion* = little sack, *colon* = terminal portion of the intestine.
2. **Geographic distribution/epidemiology**: Worldwide, however, rather few cases (<1000) were diagnosed in humans per year.
3. **Biology, morphology**: The protozoan parasite *Balantidium coli* is characterized by its typical surface provided with rows of cilia and by the presence of two nuclei (one macro- and one micronucleus – Fig. 3.53). It measures 30–150 μm in length and 25–60 in width and lives as (mostly)

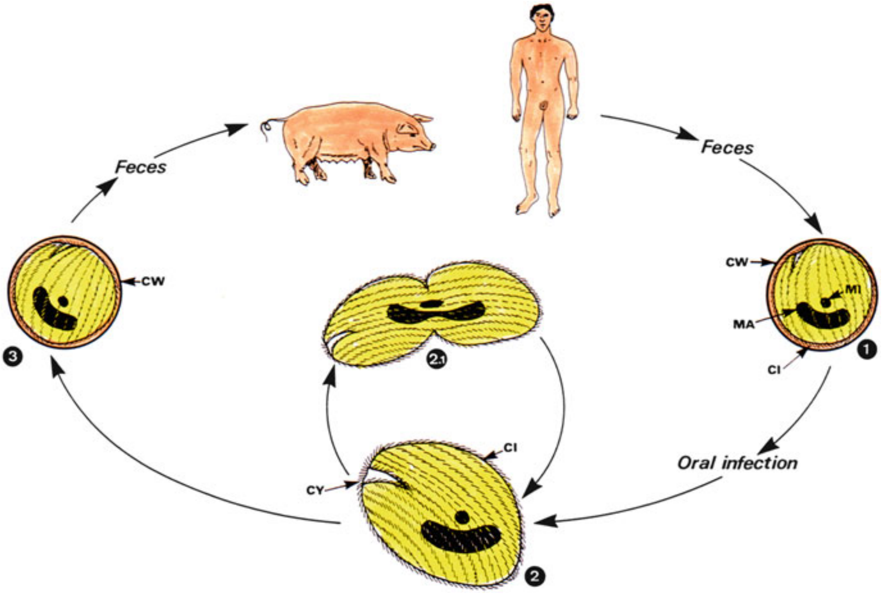

Fig. 3.53 Diagrammatic representation of the life cycle of *Balantidium coli*. The infection occurs by oral uptake of cysts from feces of pigs. (**1**) Cyst outside bodies – excreted by pigs or infected humans. (**2**) After oral uptake, parasites hatch from the cyst inside the intestine and starts binary fissions (**2.1**). (**3**) Production of cysts inside the host and excretion within feces. *CI* cilia; *CW* cyst wall; *CY* cytoplasm; *MA* macronucleus; *MI* micronucleus

harmless parasite in the caecum and colon of humans. Especially endangered are workers in slaughterhouses and farmers of pigs, since pigs are the main hosts. *B. coli* stages reproduce themselves by repeated binary cross divisions (Figs. 3.53, 3.54). Under conditions not yet understood, these parasites may enter the intestinal wall (Fig. 3.54). After a series of binary divisions, the stages inside the colon excrete a rather stiff wall. The thus formed spherical cysts which have diameters of about 50–70 µm were excreted within the feces, from where they become transmitted to other hosts by direct contact with feces or with the help of flies, which may transport them onto food.

4. **Symptoms of the disease (Balantidiasis, *Balantidium* flu)**: In most cases an infection with *B. coli* remains hidden and undiscovered. In cases of ingestion of large numbers of cysts, however, symptoms may occur which are similar to **bacterial** or **amoebic flu**. In these cases bloody and slimy feces were excreted 8–12 times per day after an incubation period of about 4 days. Further symptoms are spasms, dizziness and vomiting. Later, when the disease enters a chronic stage, intermittent phases of diarrhoea and obstipation occur. **Attention**: If these severe infections are not treated, peritonitis may occur endangering the life of the patient.
5. **Diagnosis**: Microscopic demonstration of motile stages in fresh, warm feces and cysts with the help of concentration methods such as MIF, SAF or flotation.

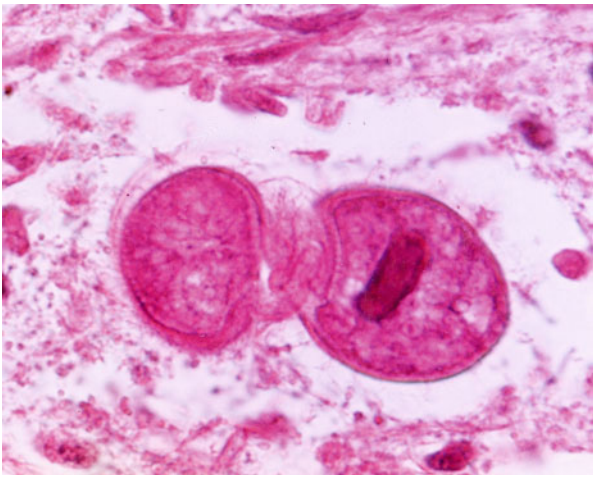

Fig. 3.54 Light micrograph of two ciliated stages of *Balantidium coli* inside the intestinal wall

6. **Pathway of infection**: Oral uptake of cysts within fecally contaminated food or drinking water. Furthermore infections may occur when handling intestines of slaughtered pigs by farmers, butchers or hunters. Cysts may also be found on fecally contaminated salad leaves.
7. **Prophylaxis**: Avoidance of contact to feces of humans and pigs.
8. **Incubation period**: Days until weeks.
9. **Prepatent period**: 4 days until weeks.
10. **Patency**: Eventually years.
11. **Therapy**: The use of nitroimidazoles: e.g. metronidazole, 3 × 750 mg daily in the case of adults, 35–50 mg/kg bodyweight divided into three dosages daily for 5 days in the case of children **or** tetracyclines (4 × 500 mg for 10 days).

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3.19 *Pneumocystis jiroveci* (Pneumocystosis)

1. **Name**: Greek – *pneuma* = air; *kystos* = cyst; *jiroveci* = name honouring the Czechoslovakian scientist **Jirovec**, who first described the stages in humans, while the Italian researcher **Carini** described *P. carinii* occurring mainly in rats.
2. **Geographic distribution/epidemiology**: This species occurs worldwide in humans and probably also in a wide range of animals (where *P. carinii* was described). It is found inside the lungs, where it intensively reproduces and leads to death in up to 40 % of infected immunosuppressed persons.
3. **Biology, morphology**: The parasite occurs worldwide very frequently in the lungs of humans (Frenkel 1976). In the cases of immunosuppressed or cortisone-treated persons, this parasite leads to death in about 40 % of the infected persons. According to investigations of the RNA of this parasite, it should belong to the fungi; however, according to the appearance of its mitochondria, nuclei and Golgi apparatus, to their reaction on sulphonamides and to the type of their division process, it is closely related to amoebae (protozoa). Perhaps it is only a remnant of an ancient group. The developmental stages of this parasite appear mostly spherical and measure only 3–8 μm in diameter (Fig. 3.55). The full life cycle, which was first shown by Yoshikawa et al. (1987), is now widely confirmed. According to this description, haploid trophozoites first occur. After a phase of constant divisions, two of these trophozoites fuse forming a diploid cyst, which produces a rather thick cyst wall. Inside this cyst meiosis occurs leading finally to eight daughter cells (=small trophozoites), which still in the same host's lung (especially in the case of immunocompromised persons) hatch and may start new reproduction. However, such cysts also appear in coughed up material, which thus may infect other hosts.
4. **Symptoms of the disease (Pneumocystosis)**: In general immunocompetent humans do not show symptoms, which, however, occur in immunosuppressed persons. These symptoms start with reactions similar to a lung inflammation together with a rather low fever. The ongoing symptoms are characterized by increasing problems to get enough oxygen, since the parasites finally cover fully the surface of the lung alveoles, thus introduce the production of a slimy mucus that finally blocks the uptake of sufficient oxygen.
5. **Diagnosis**: The so-called *Pneumocystis* pneumonia can be best diagnosed by microscopic investigation of the lavage material from the lung. 10 ml of this material (evtl. added by 0.9 % NaCl solution) has to be centrifuged (1500 g/ 5 min). From the sediment a smear preparation is made and coloured according to the method of Grocott, which represents a silver staining that shows the wall of most developmental stages. Other colourations (e.g. toluidine, Giemsa, Gram-Weigert) are less good. The trophozoites of this species may also become detected in fresh sputum (obtained after inhalation of 3 % NaCl solution). Immunocytological stainings (e.g. immunofluorescence/peroxidase combined with monoclonal antibodies) can be done rather quickly. DNA of

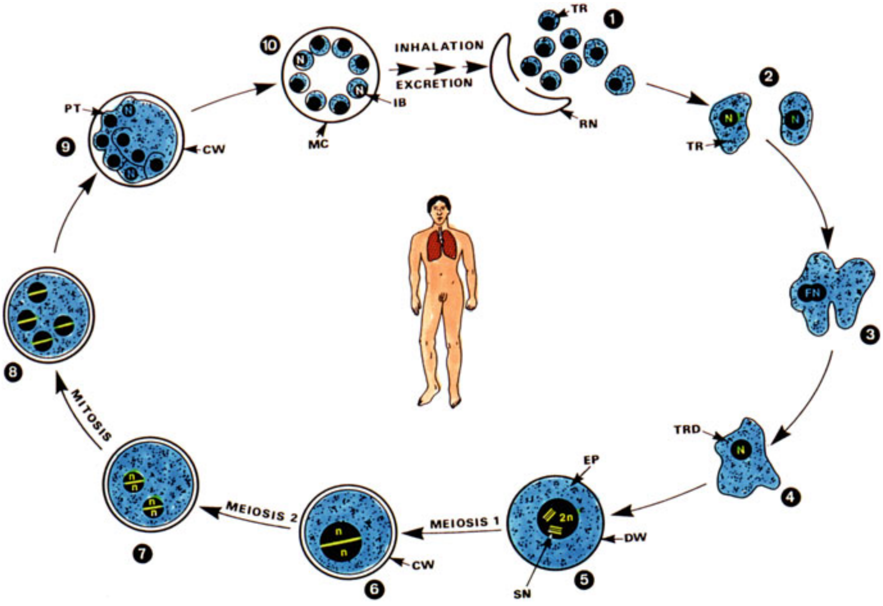

Fig. 3.55 Diagrammatic representation of the life cycle of *Pneumocystis jiroveci*. (**1**) Immunocompromised persons inhale tiny cysts from infected persons. Inside their lungs eight trophozoites hatch from each cyst. (**2–4**) Always two trophozoites fuse and thus form a zygote, which may become divided repeatedly into two new stages. (**5**) Zygotes start encystation by forming a wall. (**6–8**) Formation of eight nuclei. (**9**) Formation of eight young trophozoites. (**10**) Mature cyst with a new generation of intracystic bodies. *CW* cyst wall; *DW* developing cyst stage; *EP* early cyst; *FN* fusion of nuclei; *IB* intracystic body; *MC* mature cyst; *N* nucleus; *PT* protrusion; *RN* remnants of plasma; *SN* synaptonemal complex; *TR* trophozoites (haploid); *TRD* trophozoites (=diploid)

P. jiroveci may be determined within sputum with the help of polymerase chain reaction (PCR). The determination of antibodies is not helpful, since they give no significant information.

6. **Pathway of infection**: Probably inhaling parasite-contaminated droplets excreted by saliva or coughing of infected persons.
7. **Prophylaxis**: Immunosuppressive persons should avoid close contact to coughing persons.
8. **Incubation period**: About 1 week (depending on the amount of inhaled infectious stages).
9. **Prepatent period**: About 1 week.
10. **Patency**: Years!
11. **Therapy**: Very common is the treatment using cotrimoxazole (100 mg/kg bodyweight given in three doses per day for 3 weeks). Pentamidine is also very effective (4 mg/kg bodyweight daily iv or im for 3 weeks). Further possibilities are offered by trimethoprim/dapsone, clindamycin/primaquine,

trimetrexate, atovaquone, eflornithine and pentamidine inhalation. Furthermore is proven the efficacy of epiroprim/dapsone. In cases of hypoxia ($pO_2 < 70$ mg Hg) and severe diseases, corticosteroids should be given initially.

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3.20 *Blastocystis* Species (Blastocystosis)

1. **Name**: Greek – *blastos* = germ, vesicle; Latin: *homo* = human.
2. **Geographic distribution/epidemiology**: Worldwide, up to 20 % prevalence in healthy persons, up to 50 % in HIV patients.
3. **Biology, morphology**: *B. hominis* stages are known since many years from stool investigations from healthy persons as well in Europe as well as from people in the tropics. The stages observed showed two different stages (trophozoites and cysts (Figs. 3.10, 3.11). Many trophozoites reached only a size of 5–20 μm in diameter and contained a large vacuole, which cannot be stained with the help of iodine or eosin. Furthermore the peripheral cytoplasm contained many flattened nuclei. Apparently these trophozoites could increase their size up to 200 μm in diameter by a not yet described method. Divisions apparently occur by a type of budding whereby one to two daughter cells are formed at the same time (Fig. 3.56a, c). Cysts reach a maximum size of 30 μm in diameter and are characterized by a nucleus which appears as a whitish region. The trophozoites are in general contained in slimy up to fluid feces and may reach enormous amounts. For a long time, *B. hominis* was considered as an apathogenic fungus. Many investigations of the groups of Zierdt, Yoshikawa and Tan, however, showed that this organism might be an ancient protozoan, which is a facultative pathogenic in immunocompromised persons. Electron microscopic investigations on the other side revealed indications that there are mainly morphologic similarities to fungi. Thus even today the correct status of this organism remains undetermined.
4. **Symptoms of the disease (Blastocystosis)**: These stages are found as well in normal feces but also in diarrhoeic ones, which were accompanied by bloody diarrhoeas, heavy abdominal pain, vomiting and inappetence. In the case of

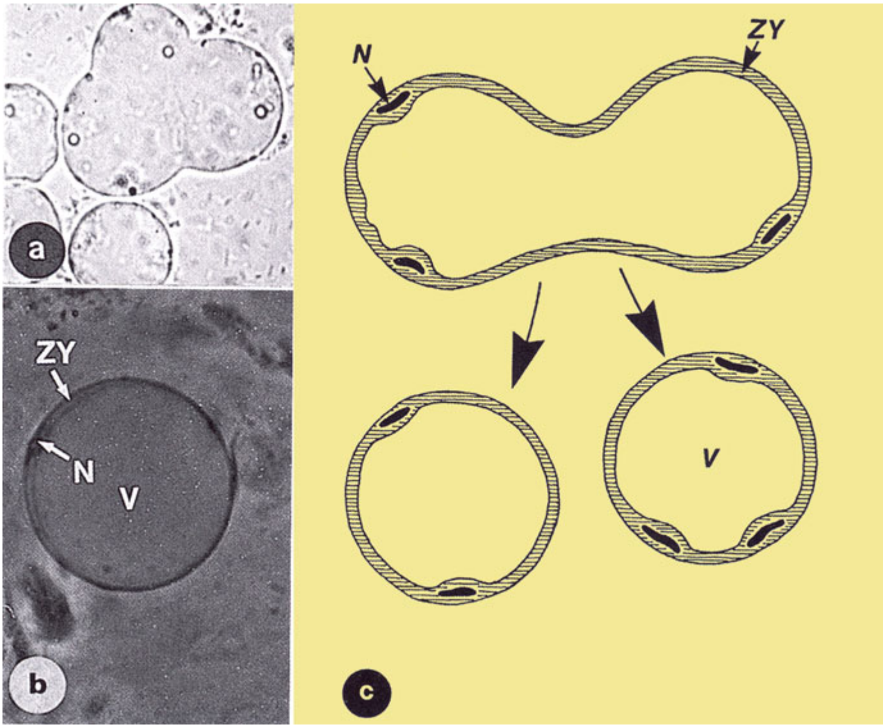

Fig. 3.56 *Blastocystis*: light micrograph (**a**, **b**) and a diagrammatic representation of the division of trophozoites (**c**) according to Zierdt. *N* nucleus; *V* vacuole; *ZY* cytoplasm

immunocompromised people, diarrhoeas were noted with excretion up to 8 l of feces per day. However, also fully symptomless people were found to excrete large members of such stages.

5. **Diagnosis**: Microscopic determinations of trophozoites and cyst stages obtained in fresh feces and/or in probes after concentration by methods like MIFC or SAF (Fig. 3.45).
6. **Pathway of infection**: Apparently by oral uptake of cysts within contaminated food or within drinking water. It was also shown that pig feces contained similar stages in large numbers.
7. **Prophylaxis**: Especially children and immune-deficient persons should avoid any contact to human and/or animal feces.
8. **Incubation period**: Apparently 2–3 days in experimentally infected pigs, however unknown in humans.
9. **Prepatent period**: Estimated, several days.
10. **Patency**: 2–3 weeks; however, data are not sound since a symptomless phase may be long.
11. **Therapy**: In case of the above-described symptoms and after exclusion of other infections, treatment can be done by oral application of metronidazole (3 × 750

or 4 × 500 mg daily for 5–7 days). Cotrimoxazole was also helpful (2× daily 160 mg trimethoprim/800 mg sulfamethoxazole). Children: 6–30 mg/kg bodyweight for 7–10 days. However, in both cases of medicaments, not all symptoms and *Blastocystis* stages may disappear.

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3.21 Microsporidia

This is probably the most ancient protozoans, where many features of the today-existing (mostly highly differentiated) parasite are lacking. Their roots are apparently close to the base of the origin of the first cells on earth.

3.21.1 *Enterocytozoon bieneusi* (Enterocytozoonosis)

1. **Name**: Greek – *enteron* = intestine; *kytos* = cell; *zoon* = animal. Bieneus = family name of the first patient (a woman from Haiti).
2. **Geographic distribution/epidemiology**: Worldwide. This species covers today about 40 % of the human cases of microsporidian infections. About 10 % of the HIV patients suffer from infections with microsporidia.
3. **Biology, morphology**: The merogony (=schizogony) and sporogony (=formation of spores) of this species occurs inside the cells of the small intestine (enterocytes and cells of the lamina propria). In some HIV patients, up to 50 % of the cells have been infected as it was seen in necropsies. Recent investigations showed that these parasites may also develop inside the lung cells. The merogonic phase of reproduction involves binary divisions of two-nucleated stages of 3–4 μm in diameter, while the sporogonic divisions lead to eight daughter cells deriving from eight nuclei-containing cells. The spores (=infectious stages) measure 1.5 × 0.5 μm. Their polar filament shows five windings when retracted inside the cell (=not yet protruded). The so-called endospore is rather smooth. The life cycle is similar to that of *Encephalitozoon cuniculi* depicted in Fig. 3.57, showing that the infection starts by ingestion of spores with fecally contaminated food. However, in cases of HIV patients, hatching of the sporoplasm apparently occurs already in their intestine, so that repeated mass infections may occur. Of the 14 known human-pathogenic microsporidian species, *E. bieneusi* is the most common one. Today, over 200 *E. bieneusi* genotypes are described; however, humans are predominantly

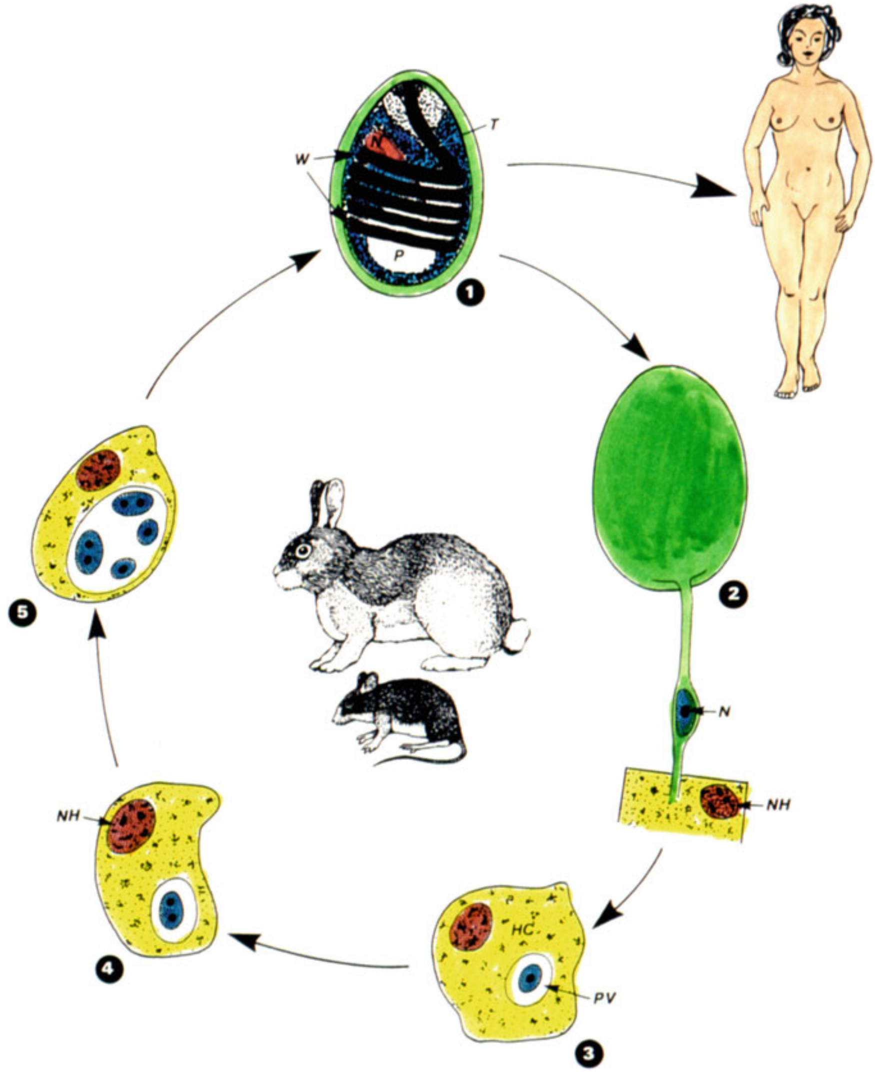

Fig. 3.57 Life cycle of *Encephalitozoon cuniculi*, which may parasitize within a variety of hosts including immune-depressive humans. (**1**) The infection of AIDS patients occurs via oral uptake of spores that derive from urine of animals (via contaminated food or via touching of furs). The mature uninuclear spore is characterized by five windings of the polar tube (**1**) and the occurrence of a posterior vacuole (P). (**2**, **3**) In human intestine the spore extrudes the polar tube which is injected into a host cell. The uninuclear sporoplasm creeps through the tube in the cytoplasm of the host cell, where it is included within a parasitophorous vacuole. (**4**, **5**) Reproduction by repeated binary fissions. The last binary fission (5) leads to two uninuclear sporoblasts, which each growing up and differentiating into an infectious cyst. The latter are set free when the host cell is used up and bursts. Thus these spores may become distributed in the whole body or set free in human stool. *HC* host cell; *N* nucleus; *NH* nucleus of host cell; *P* posterior vacuole; *W* windings of the polar tube; *T* polar tube

infected with stages from group 1 genotypes (CD, EbpC, type IV, etc.) and only sporadically with the genotypes BEB4, I, J and Nig5.

4. **Symptoms of the disease (Microsporidiosis)**: Typical symptoms are intermittent, watery diarrhoeas (without blood!) with weakness, which may occur three to ten times per day for up to 5 months. This leads to severe weight losses and introduces painful contractions of the belly and often additional fevers. These symptoms may become intensified if double infections together with *Giardia lamblia* occur. This disease was also detected in numerous non-HIV patients coming back from travels to the tropical regions.
5. **Diagnosis**: Microscopic determination of spores taken from fluid feces or by microscopic analysis of biopsies taken from the intestinal surface.
6. **Pathway of infection**: Unknown; however, the ingestion of spore-contaminated food is the most probable explanation. Autoinfection is apparently very common especially in the case of persons with immunosuppression.
7. **Prophylaxis**: Avoidance of contacts to feces, washing of fruits and salad before eating.
8. **Incubation period**: About 1 week.
9. **Prepatent period**: Longer than 5 weeks.
10. **Patency**: 2–3 weeks.
11. **Therapy**: Unknown; however, albendazole trials had a significant efficacy in a range of patient who had ingested doses such as 2 × 400 mg/daily. Also metronidazole (1–2.5 g daily) and cotrimoxazole showed efficacy in other patients. A complete cure, however, was not reached. **Very important**: Replacement of water loss and loss of electrolytic substances.

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3.21.2 *Septata intestinalis*

1. **Name**: Latin, *septum* = separating wall, layer; *intestinalis* = belonging to the intestine.

   The stages of this species parasitize cells of the whole intestine as well as those of the urogenital system. The definitive life cycle of this species first described in 1993 is not well clear in many phases, although the specimens had been found worldwide in a very large number of HIV patients, where apparently about 2.2 % of the total number of diarrhoeas were induced by this agent of disease.

2. **Therapy**: In all cases treated with albendazole (400 mg/day for 4 days), this cure led to the disappearance of all symptoms of disease and stopped the excretion of spores.

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3.22 *Encephalitozoon cuniculi* (Encephalitozoonosis)

1. **Name**: Greek – *encephalon* = brain; *zoon* = animal. Latin: *cuniculus* = rabbit.
2. **Geographic distribution/epidemiology**: Worldwide, mostly diagnosed only in immunosuppressed humans; several hundred thousand humans are infected.
3. **Biology, morphology**: The ovoid infectious stages (=spores) of this species reach a size of about 2.5–5 μm (Fig. 3.57). As soon as the spore has arrived in the intestine, the hollow polar tube is extruded and penetrates into an intestinal cell. The parasite's cytoplasm creeps through this tube into the host cell cytoplasm and starts reproduction within a freshly formed parasitophorous vacuole, so that finally several new spores are produced. These stages were set free as soon as the degenerating host cell becomes disrupted. Within the feces these infectious spores are set free and may infect other hosts. However, especially in the case of immunosuppressed persons, these spores may extrude the polar tube even inside the same host thus introducing a massive infection. There are described several serotypes, which occur besides in humans and rabbits also in dogs and monkeys.
4. **Symptoms of the disease (encephalitozoonosis)**: While in rodents the symptoms of disease remain rather mild and lead to a chronic infection, in humans (especially children and immunosuppressed persons) and monkeys, dogs and foxes, a very fulminant disease occurs, described as "encephalitis-nephritis syndrome", which may lead to death. In addition severe infections of the eyes may occur, where large lesions are induced in the walls of the eye arteries.
5. **Diagnosis**: Microscopic determination of the spores within centrifuged urine. In sections of the infected organs, spores and developmental stages can be

diagnosed with the help of colourations (e.g. Gram, haematoxylin eosin, methenamine silver). Serologic tests (IFAT, KBR, ELISA, etc.) are not very specific and detect only about 70 % of the infections.

6. **Pathway of infection**: Oral or nasal uptake of wind-drifted spores from urine or dry feces of animals or humans. However, congenital and diaplacentary transmissions seem to be possible, too.
7. **Prophylaxis**: Avoidance of mouth-to-body contact with animals; avoidance of contacts to urine and feces of humans and animals; washing of fruits.
8. **Incubation period**: In children and immunosuppressed people, only a few days.
9. **Prepatent period**: Unknown, but apparently short.
10. **Patency**: Apparently months in chronic cases.
11. **Therapy**: Unknown, however, in vitro tests showed that chloroquine and oxytetracycline reduced considerably the spore formation. In the case of other microsporidia, albendazole was very effective (2 × 400 mg/day for 21 days).

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3.23 *Encephalitozoon intestinalis* (Encephalitozoonosis)

The 1–2 µm sized spores of this species, which mainly occurs in ruminants and birds, were also found in immunosuppressed persons. The biology and transmission are similar to that of *E. cuniculi*.

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3.24 *Nosema connori* (syn. *conneri*) (Nosematosis)

1. **Name**: Greek – *nosos* = disease. Connor = American scientist.
2. **Geographic distribution/epidemiology**: Worldwide among people suffering from immunosuppression.
3. **Biology, morphology**: This species of microsporidians is until today exclusively found in persons with immunosuppression and may lead (often in combination with a *Pneumocystis* infection) to death. The infectious spores measure 4 × 2 µm and are characterized by a PAS-positive polar body and by nuclei, which are situated closely side by side. The development of the spores was seen in the heart muscle, in the walls of the intestine and the stomach, but also in the liver, lung and nerve system thus is spread practically all over the body.
4. **Symptoms of the disease (Nosematosis)**: The strongly weakening phase of disease leads very often within 4 months to death based on the loss of function of the parasitized organs. Diarrhoeas and severe lung symptoms are also very common.
5. **Diagnosis**: Microscopic demonstration of the spores inside the urine and in the feces after concentration methods such as MIFC or SAF
6. **Pathway of infection**: Ingestion or inhaling of the infectious spores from feces of humans and probably also from animals.
7. **Prophylaxis**: Avoidance of contact with pet animals and human and animal feces.
8. **Incubation period**: Unknown.
9. **Prepatent period**: Unknown.
10. **Patency**: Without treatment, lifelong.
11. **Therapy**: In tests penicillin plus sulfisoxazole had been successful; in the case of other microsporidia, albendazole showed promising effects.

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Worms of Humans

4

4.1 What Are Worms?

The groups of parasites, which are shown in the following Sects. 4.1 up to 4.5, are generally summarized as **Helminths** = worms. Although they all may look more or less like worms, they have no close similarities either in their inner organization or in their reaction on chemotherapeutics. Their life cycles are different from those of the Protozoa (Chap. 3), because most of them do not multiply immediately in their final hosts. There are only as many stages developed to adults as larvae or eggs have reached the host (e.g. by contaminated food). Proliferation may take place in the intermediate hosts (e.g. in the case of Trematodes). Great progress has been made in the last years concerning medical treatment of worm-borne diseases, so that today several effective and safe medications exist. These will be presented in the following sections. However, more and more resistances of parasites against drugs become recently noted. Therefore, intense care has to be taken on proper use (times, dosages). Furthermore, the search for new classes of active substances is vividly important. Also the development of alternative medications is needed. The result would be that the present drug resistance of several parasite populations will disappear after some time.

The most important species of worms parasitizing humans belong to the so-called **Platyhelminthes** (with the groups **Trematoda** (=flukes) and **Cestoda** (=tapeworms) as well as the so-called **Nemathelminthes** (former: Aschelminthes), which are better known as roundworms.

4.2 Trematodes (Flukes)

The class of trematodes includes only such parasites, which anchor themselves at the inner or outer surface of their hosts by the help of their hold-fast apparatus (suckers). The particularities of this attachment system were used to systematize the trematodes (besides some other specialities in their life cycle).

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According to the traditional system **Trematodes** include the following groups:

- Aspidobothrea
- Monogenea
- Digenea

According to other systems only the following groups are included:

- Aspidobothrea
- Digenea

However, there exist many other proposals which are based on different data used. Therefore, it seems reasonable to consider in this short textbook, which comprises only very important parasites of humans, exclusively species which belong to the class of **Digenea** that all possess a complicated and sophisticated life cycle comprising a follow-up of several, mostly differently looking generations.

The term **Digenea** (=two generations) was created to characterize species, which have developed during their life cycle the typical alternation of generations being accompanied by an obligate change of hosts. Their life cycles are mostly very complicated. Thus, it is difficult to establish a uniform systematic classification without consideration of inner (however badly visible) organ structures. Thus, exclusively outer morphological criteria are used to differentiate the groups of flukes, which in all cases do not possess an anus.

1. **Gasterostome flukes**

   The intestine looks sack-like and has no branches, and the mouth has no apical but a ventral opening.
2. **Monostome flukes**

   One of the mostly two existing suckers is reduced (in general the ventral one).
3. **Distome flukes**

   The ventral sucker exists, but its position varies (depending on the species) from a place close to the apical pole until the posterior pole.
4. **Amphistome flukes**

   The second sucker occurs exactly at the posterior pole.
5. **Echinostome flukes**

   The oral sucker is surrounded by species-specific rows of hooks.
6. **Holostome flukes**

   These flukes have in addition to the two suckers another hold-fast system developed—the so-called **tribocytic organ**.

   All these above listed flukes (**1**–**6**) are **hermaphrodites**—they contain both male and female sexual organs. The flukes of the last—7th group, however, are dioecious: they possess male and female adult worms.
7. **Schistosomes** (Greek: *schizein* = divide; *soma* = body)

   In this group the leaf-like looking males surround (forming a channel) the slender long female and keeps her there lifelong (up to 25 years!).

Simplified system	
Class	**Trematodes**
Subclass	**Digenea**
1. Superorder:	Anepitheliocystidia (embryonal excretion bladder remains active)
Order:	Strigeata (cercariae possess a bifurcated tail, their miracidia contain two protonephridia = excretion organs)
Family:	– Strigeidae
	– Diplostomatidae
	– Schistosomatidae
	– Spirochidae
	– Cyclocoeliidae
	– Bucephalidae
	– Others
Order:	Echinostomata (cercariae possess a non-birfurcated tail, miracidia have only one single protonephridium)
Family:	– Fasciolidae
	– Gastrodiscidae
	– Paramphistomatidae
	– Others
2. Superorder:	Epitheliocystidia (the excretion bladder is newly formed from mesodermal cells, tail of cercariae not bifurcated)
Order:	Plagiochiata (cercariae may possess a terminal boring stiletto and their tail contains only occasionally excretion channels)
Family:	– Dicrocoeliidae
	– Plagiorchiidae
	– Prosthogonimidae
	– Troglotrematidae
	– Others
Order:	Opisthorchiata (cercariae possess always channels for excretion, never occurs an oral stiletto)
Family:	– Opisthorchiidae
	– Heterophyidae, etc.

4.2.1 *Schistosoma haematobium*, Bladder Fluke (Bladder bilharziasis)

1. **Name**: Greek: *schisis* = splitting; *soma* = body; *haima* = blood; *bios* = life.
2. **Geographic distribution/epidemiology**: Large areas in Africa with rivers: North-western to North-eastern Africa, delta of the Nile up to its spring, floodplains of Eastern and Western Africa, the Western side of Madagascar, Arabian Peninsula, Iraq as well as some small spots in India. Recently, an outbreak was recorded on the island of Corsica in the Mediterranean Sea.

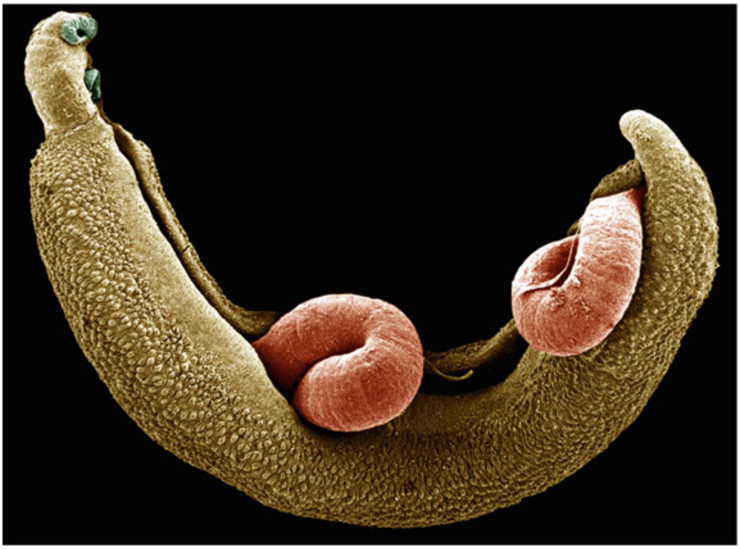

Fig. 4.1 Scanning electron micrograph of a couple of the species *Schistosoma mansoni*. The male transports the female inside the so-called canalis gynaecophorous, which is produced by upfolding of the lateral sides of the male

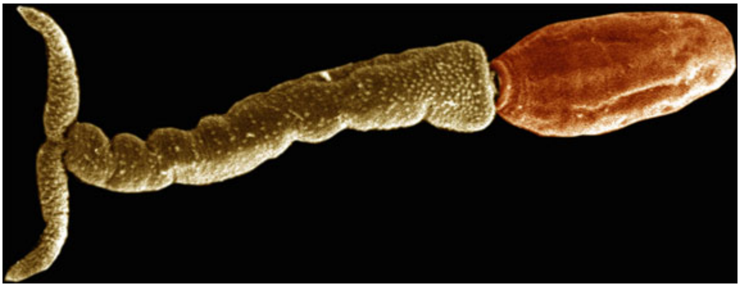

Fig. 4.2 Scanning electron micrograph of a cercaria of *S. mansoni*

3. **Biology, morphology**: Adult worms of *S. haematobium* are bisexual as are all schistosomes (Trematoda, Platyhelminthes). They live in permanent copula; the 1.5 cm long flattened male carries the round female (up to 2.5 cm long) in his ventral fold (canalis gynaecophorous). These couples stay in the venes of the urogenital system and bladder of their human hosts (Figs. 4.1 and 4.2). Every day the female lays 300 eggs, which are quite big (110–170 μm × 70 μm) and possess a small terminal spike (Fig. 4.3). These eggs penetrate the bladder wall being supported in this process by proteases excreted by the contained miracidium larva. As soon as the egg reaches the mucosa of the bladder, it can be observed endoscopically inside a whitish pseudotuberculum of 1–2 mm in

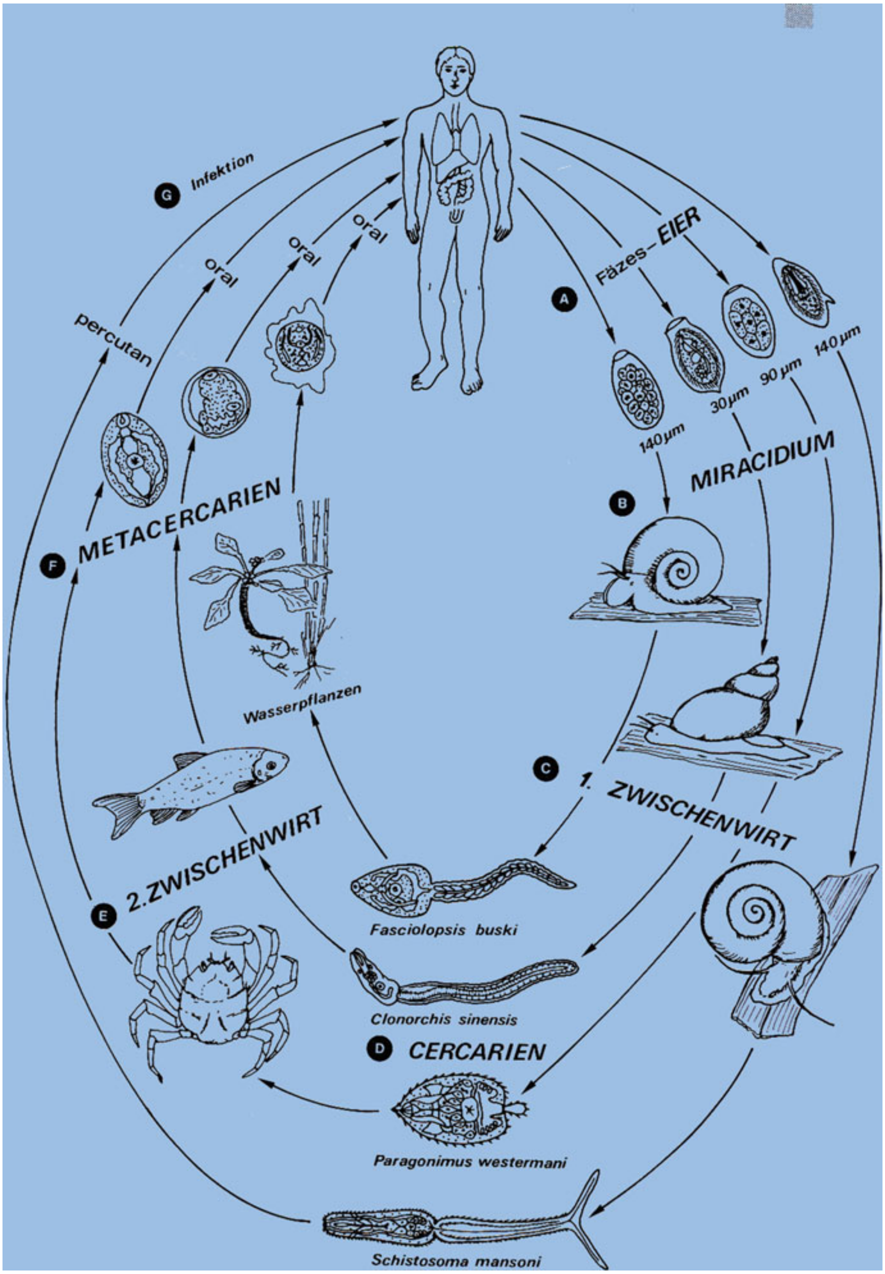
G Infektion
percutan
oral
oral
oral
A
Fäzes-EIER
140 µm
30 µm
90 µm
140 µm
B
MIRACIDIUM
F METACERCARIEN
Wasserpflanzen
C
1. ZWISCHENWIRT
E
2.ZWISCHENWIRT
Fasciolopsis buski
Clonorchis sinensis
D CERCARIEN
Paragonimus westermani
Schistosoma mansoni

Fig. 4.3 Life cycle of four important trematode species. Eier = eggs; Faezes = feces; Zwischenwirt = intermediate host; Cercarien = cercariae; Infektion = infection

size. When the egg reaches freshwater within human urine, the miracidium hatches, starts swimming, searches and penetrates actively into water snails. In the hepatopancreas of the snail (=intermediate host), a proliferation process via sporocysts takes place. The daughter sporocyst generation finally produces many larvae, the so-called bifurcated cercariae. These stages leave the snail and have to find their hosts in the water within 24–48 h. In the case that humans are working on paddy fields or bathing in the contaminated water, they may become infected. While penetrating the skin of the human host, the cercariae throw off their "tail". After a time in the skin (as so-called **schistosomulum** stage and later in the lung adapting to the immune system of the host), the parasites finally take their way via blood vessels to the urogenital system. There the female will get sexually mature only 5–6 weeks after constant copulation. This pair is able to fix itself in the blood vessels by using their two big suckers at the mouth and belly of the male bearing the female inside the so-called canalis gynaecophorus.

4. **Symptoms of the disease (Schistosomiasis of the bladder, bladder bilharziasis)**: The severity of the disease depends on the number of pairs of parasites, which may live for about 25 years. In general the following symptoms are shown:
   (a) **Pruritus** at the entry point of the cercariae at the skin; repeated infection may lead to a **cercaria dermatitis**.
   (b) In the case of a first infection, an **unspecific fever** occurs after 4–7 weeks as a general reaction of the host's sensibilization.
   (c) Eggs are found in the urine starting about 2–3 month after infection (maybe also only after 2 years). Bloody traces (=**haematuria**) are observed especially in the last portion of the urine. The patient complains burning in the urethra and urinary urgency.
   (d) The further chronic course of the disease does not show blood and eggs all the time. Therefore, it is recommended to repeat the investigation of the urine, if the test was negative primarily.
   (e) During bladder inspection with a cystoscope egg granulomas may be observed (pseudotubercles) at the bladder wall. They appear as whitish nodules of 1–2 mm in diameter (Fig. 4.4).
   (f) *S. haematobium* infections show the following complications:
      - Secondary bacterial infections of the bladder due to incomplete emptying. This causes granuloma-borne fibrosis and calcification. In this case, the contraction ability of the bladder will become reduced.
      - Ulcers (maybe also carcinoma of the bladder wall) occur due to permanent tissue irritation.
      - Alteration of the genitalia (so-called elephantiasis by chronic oedema) has also been observed. A swelling of the liver can be found as well due to formation and growth of granulomas.

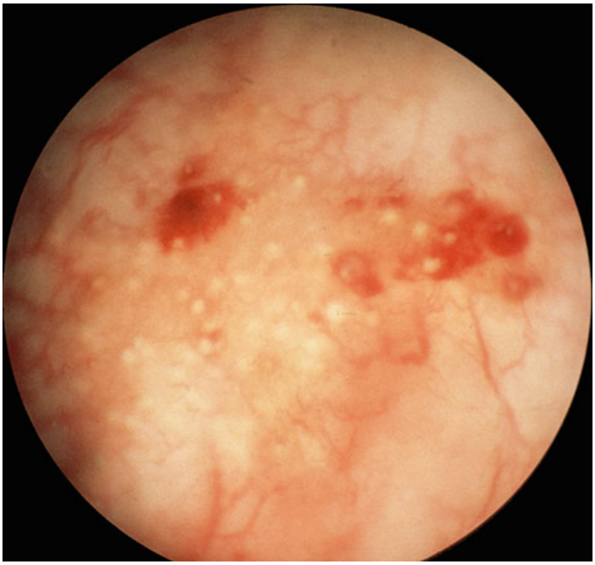

Fig. 4.4 Inside aspect of the urinary bladder of a female patient. The bladder wall shows *whitish* protrusions deriving from protruding eggs of *S. haematobium* and typical bleedings at places where eggs already had left the bladder wall

5. **Diagnosis**: The typical eggs (equipped with a terminal thorn; Fig. 4.5) can be observed in the urine and in biopsies of the bladder, but only rarely in the feces. In the case of an enormous infection, the proof of the eggs in the urine may be successful in the spontaneous first portion of the urine as well as in cases of quantitative examination of the sediment obtained from the latest urine portions. Since the daily excretion of the eggs always varies, a repeating of the test procedure is strongly recommended as well as the investigation of the sediment of the total urine after centrifugation. The excretion of the eggs has its peak at noon and after body workout (urine collecting is recommended between 10 a.m. and 2 p.m.). If the urine cannot be investigated immediately within 1–2 h, 1 ml formalin (37 %)/100 ml urine has to be added to prevent the miracidia from hatching.

   The investigation of larger amounts of urine after collection over 24 h should be done as follows: sedimentation for 1 h in a large glass vessel (in the case of huge amounts of sediments, it is necessary to wash them with cold 1 % NaCl solution several times), decantation, centrifugation of the remnant fluid (max. 2000 g for 2 min) and microscopical investigation of the sediment. Smaller amounts of urine (e.g. the last 10–50 ml sized portion of urine from noon) can be filtered. Filtering is done by the help of a polycarbonate filter (nylon or paper can be used as well) with 25 μm diameter and a pore size of 12–20 μm. The filtered material is transferred onto a glass slide (after staining by Lugol's solution) and can be examined for eggs microscopically at a low magnification (40–100×). In the case of studying unfixed material, the vitality of the eggs can be decided by observation of the motions of the cilia of the miracidium by the help of the miracidium hatching test or after supravital coloration with 0.5 % trypan blue. The proof of the eggs in biopsates can be documented by the help of a squeezing preparation (see also intestinal schistosomiasis).

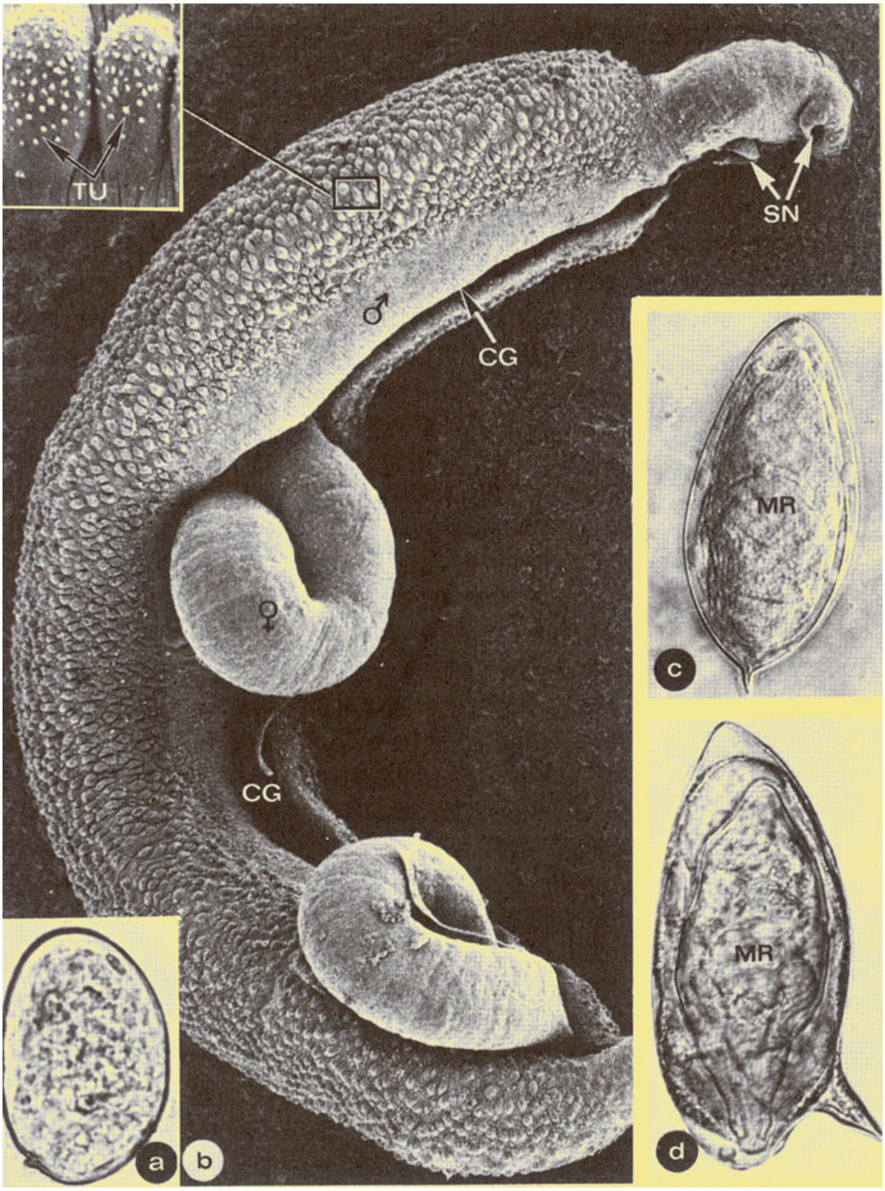

Fig. 4.5 Microscopical features of schistosomal stages. (**a**) Egg of *Schistosoma japonicum* (LM) **Upper inset:** Enlargement of the bulbous-like protrusions (with hooks) of the surface of the male worm. Fig 4.5e: Light micrograph of a section through a liver granuloma containing an egg of *S. mansoni*. The liver is degenerating here and closely filled by the blue appearing collagen fibres. (**b**) Couple of *S. mansoni* (SEM), (**c**) Egg of *S. haematobium* (LM), (**d**) Egg of *S. mansoni* (LM). *CG* canalis gynaecophorous, *LM* light microscopy, *MR* miracidium inside the egg, *SEM* scanning electron micrograph, *SN* suckers, *TU* tubercles = skin elevation bearing hooks

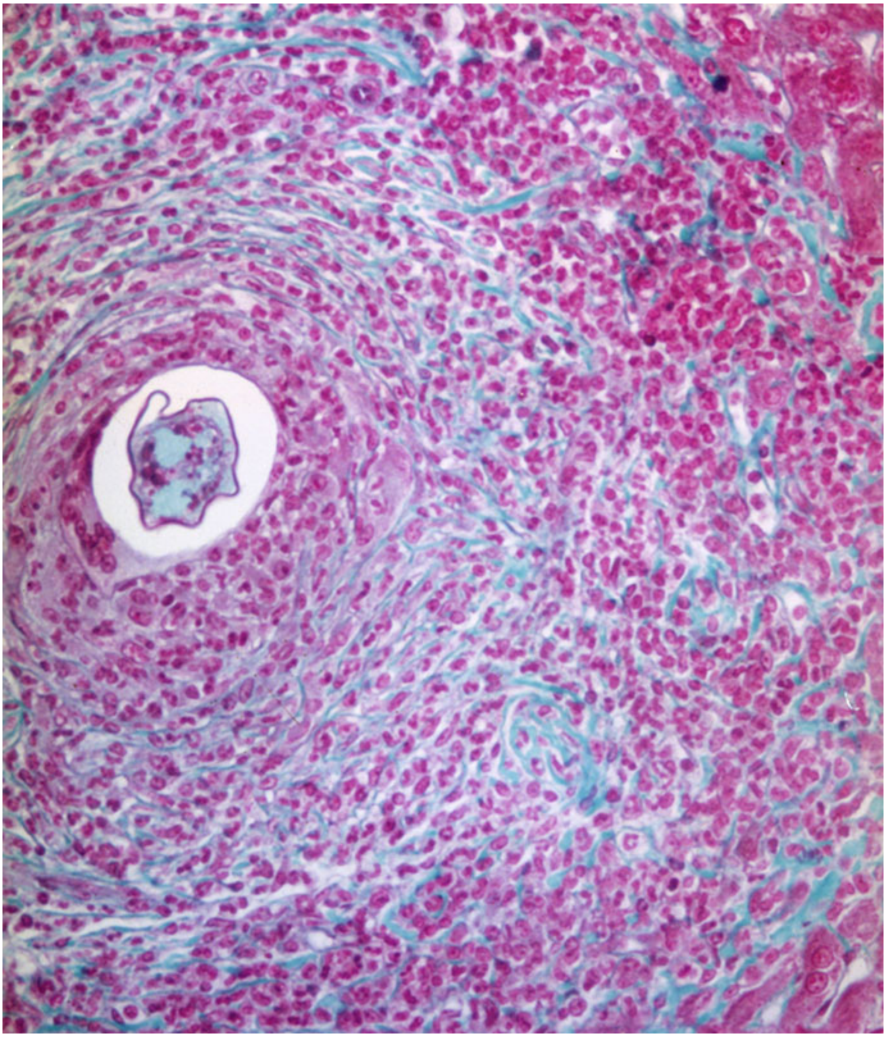

Fig. 4.5 (continued)

Immuno diagnostic: ELISA, PCR in cases of a suspected infection without proof of eggs. Eosinophilia occurs most frequently during the period of migration and during growing up of many schistosomula. In probable cases of lung and brain schistosomiasis, the use of techniques like radiology, sonography and computer tomography is recommended. This is also needed in cases of undefined fibrosis.

6. **Pathway of infection**: Percutaneously; the cercariae (shed by the intermediate hosts = water snails) penetrate into the skin of humans while they have contact with contaminated "sweet water" of rivers or lakes, wherein potential intermediate hosts live.
7. **Prophylaxis**: Avoidance of contact to potentially contaminated lakes in endemic regions. If it is needed to work in such waters, the use of boots and gloves is recommended. **Attention**: In the case of river cruises in endemic regions just wind-driven water droplets might contain infectious cercariae, since cercariae are positive phototactile and thus occur at the surface of their water biotopes.
8. **Incubation period**: Depending on the amount of worms inside a human body, symptoms of disease are noted about 4–8 weeks after an infection.
9. **Prepatent period**: 9–10 weeks, occasionally also up to 2 years (!). In cases of unisexual infections, no eggs will be found in urine.
10. **Patency**: Up to 25 years.
11. **Therapy**: The drug of choice (according to WHO) is praziquantel (40 mg/kg bodyweight) given as single dose. Metrifonate is also effective when 7.5 mg/kg bodyweight is given three times at intervals of 1 week.

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4.2.2 *Schistosoma mansoni* and Other Species (Intestinal Bilharziasis, i.e. Intestinal Schistosomiasis)

1. **Name**: Greek: *schisis* = divide; *soma* = body. The name refers to the fact that these worms are split into different sexes and are not hermaphrodites as are most of the other digenean worms. English: liver fluke, blood fluke. Discoverers: The German physician Theodor Bilharz (1825–1862) during his working period in Cairo/Egypt; the English physician Patrick Manson (1844–1932).

2. **Geographic distribution/epidemiology**: More than 200 million humans are infected; at least 600 million are endangered especially in warm regions when working in close contact with water (e.g. in rice fields, river sites, etc.)
3. **Biology, morphology**: The most common *Schistosoma* species parasitizing humans are listed in Table 4.1 besides *S. haematobium*. *S. mekongi* is now considered as own species as well as *S. malagensis* occurring in Malaysia and Thailand. *S. mekongi* has smaller adults (~16 mm in length) than *S. japonicum* and produce also smaller eggs (40–45 μm). Several species of snails act as intermediate hosts (e.g. genera *Lithoglyphobis*, *Tricula*). The adult worms are not hermaphrodites as are most of the trematodes, but males and females develop separately, however, stay together in a lifelong lasting copula. Due to this peculiar behaviour, even a very low number of penetrated cercariae will lead to a patent permanent infection. This purpose is furthermore supported by the fact that the very young worms gather in the vena portae (hepatic portal region), start copulation there and enter finally as couple in the venes of the intestinal system, where they stay lifelong for up to 25 years. The females produce daily species-specific numbers of eggs, which can be easily diagnosed by their typical large thorn (Table 4.1 and Fig. 4.5). In contrast to other trematodes, the eggs of the schistosomes have no operculum = dischargeable cover. The eggs become spread by the help of the bloodstream into the liver and in the intestinal blood vessels, where they stick and where inside their very rough egg shell the typical miracidium larva is developed in a rather short time. Around the eggs—sticking inside the capillaries—so-called **granuloma** are formed by accumulations of host defence cells. The effects of these defence cells lead to a destruction of many eggs within 6–9 months inside the granuloma (Fig. 4.5e). The total number of such tissue destructing eggs may be enormously high, since the females of *S. mansoni* may produce about 300 eggs per day and *S. japonicum* even up to 3000 (!), so that due to the long lifespan (25 years) of these worms huge numbers of eggs are accumulated. However, those eggs laying in blood vessels close to the intestinal lumen penetrate (supported by substances excreted by the miracidium inside the egg) into the intestinal lumen and are discharged within human feces. As soon as the eggs are discharged into freshwater, the enclosed miracidium larvae hatch from the egg, the shell of which becomes disrupted due to movements and secretions of the miracidium larva. This larva is highly motile, swims by the help of their surface cilia and penetrates within 1 day into a water snail, where it enters the "liver" (=hepatopancreas). Inside this organ, the miracidium is transformed into the so-called mother sporocyst, wherein so-called daughter sporocysts are developed parthenogenetically from inner undifferentiated cells. Within these daughter sporocysts, the infectious bifurcated cercariae (=forked-tailed cercariae) are developed (Fig. 4.5b). The latter are set free and swim tail forward to the surface of humans and a broad spectrum of vertebrates that have contact with water (e.g. rats, cattle, horses, donkeys, etc.). The infectious cercariae in general are set free via the respiratory aperture of the snail. They may live in the water for up to 2 days, during which they must find a suitable final host.

Table 4.1 Morphological features of *Schistosoma* species of humans

Feature	*S. mansoni*	*S. japonicum*	*S. intercalatum*	*S. haematobium*
Males, surface	Large tubercles	No tubercles	Tubercles with hook-free corona	Small tubercles with many hooks
Females, ovary	Anterior half of the body	Posterior half of the body	Behind the centre of the body	Close to the centre of the body
Number of eggs in uterus	1–10 (mostly 1)	50–300	10–20	20–100
Shape of eggs	With big lateral thorn	With small lateral thorns	With thorn at posterior end	With thorn at posterior end
Size of eggs (μm)	115–180 × 45–70	70–100 × 55–65	140–230 × 50–80	110–170 × 40–70
Occurrence	Feces	Feces	Feces	Urine
Size of worms (mm)	M: 6–12 × 1 F: 7–16 × 0.3	M: 12–20 × 0.5 F: 12–28 × 0.3	M: 11–15 × 0.4 F:10–14 × 0.2	M: 10–15 × 1 F: 20–26 × 0.3
Location of adult worms in human host	Intestinal mesenteric blood vessels	Intestinal mesenteric blood vessels	Intestinal mesenteric blood vessels	Veins of the urogenital tract
Intermediate host/snail	*Biomphalaria* sp.	*Oncomelania* sp.	*Bulinus* sp.	*Bulinus* sp.
Reservoir host	Rats, mice, monkeys	Mice, dogs, cats, pigs, cattle	Goats, sheep, rodents	Monkeys, hamsters

The ovoid eggs of *S. mekongi* do not have any thorns and are smaller (50–60 μm × 30–50 μm) than those of *S. japonicum*. In Malaysia and Thailand a new species was described as *S. malayensis*, which acts like *S. japonicum*. Intermediate hosts are species of *Tricula* snails for *S. mekongi* and *Robertsiella* snails for *S. malayensis*

M male, *F* female

4. **Symptoms of the disease (intestinal schistosomiasis, intestinal bilharziasis)**:
   (a) **Cercarial dermatitis**:

   Penetrating cercariae introduce severe itching and often skin redness, which disappear mostly within a few days (in contrast to the effects when bird schistosomes had penetrated and die at the penetration site, while the **schistosomulum** stages of human schistosomes finally enter to the liver.

   (b) **Initial fever (Katayama syndrome)**:

   Incubation period of 4–7 weeks; remittent and intermittent fevers occur accompanied by abdominal pain, swellings of the liver and spleen and dysfunction of the intestine. Simultaneously the blood examination test shows a high-grade eosinophilia.

   (c) **Blood in the feces**:

   Starting with the excretion of eggs within the feces (e.g. about 42 days after an infection in the case of *S. mansoni*, after 50–56 days in the case of *S. intercalatum* or after 30–44 days in the case of *S. japonicum*) blood can be seen on fecal excretions due to lesions along the inner intestinal wall. The amount of blood may be low, so that this occult discharge can only become diagnosed by chemical tests.

   d) **Chronic symptoms**:

   About 3–6 months after an infection, peculiar symptoms may occur, which depend on the amount of penetrated cercariae and therefrom produced worm couples.

   - **Intestinal destructions**: Diarrhoeas combined with the excretion of slime and blood may alternate with phases of obstipation. Furthermore, inflammations may occur in the colon as well as formation of so-called polyps (protrusions) in these regions.
   - **Liver damages**: Low-grade infections do introduce only low, often hidden liver symptoms. However, mass infections may introduce periportal fibrosis (pipestem fibrosis according to Symmers). An excessive fibrosis may induce atypical liver cirrhosis combined with portal hypertension, varices of the oesophagus, ascites, splenomegaly and leucopenia. Bleeding of the varices of the oesophagus or of larger liver vessels are life-threatening.
   - **Lung lesions**: Eggs drifted by the bloodstream into the lung may introduce symptoms of bronchitis, heart insufficiency, cor pulmonale and portal hypertension, which together are also life-threatening.
   - **Brain**: Due to local egg granulomas neurological dysfunctions, cramps, paralysis, diffuse encephalitis or meningitis may occur.

5. **Diagnosis**: The use of methods which show *Schistosoma* eggs (Figs. 4.5 and 4.18) is most convincing. Thus, fecal inspection methods (M.I.F., S.A.F., Kato's thick fecal smear method, sedimentation of fecal probes) are most convincing. However, several biochemical and immunological methods are especially useful in cases of low-grade infections.
6. **Pathway of infection**: Percutaneous penetration of cercariae when swimming or working in cercariae-contaminated water.

7. **Prophylaxis**: Avoidance of contacts with potentially cercariae-containing water from lakes, rivers, etc., in epidemic regions.
8. **Incubation period**:
   (a) Reactions after penetrated cercariae: 6 h until 2 days;
   (b) First reactions on pre-adult and adult worms:

S. mansoni	2–3 weeks
S. japonicum	2–3 weeks
S. intercalatum	4–7 weeks
S. haematobium	2–10 months

9. **Prepatent period**: The data of this period describe the needed time until eggs occur first in feces and in urine:

S. mansoni	4–7 weeks
S. japonicum	4–5 weeks
S. intercalatum	6–8 weeks
S. haematobium	8–12 weeks

10. **Patency**: 5–25 years.
11. **Therapy**: Drug of choice is **praziquantel**, which acts successfully against all human *Schistosoma* species. The recommended dosage is 3 × 20 mg/kg bodyweight in 1 day. **Oxamniquine** (1 × 15 mg/kg bodyweight) acts only against *S. mansoni*. In cases of the so-called Katayama syndrome, it is needed to give additionally corticosteroids. In cases of hypertension, symptoms combined with varioles along the oesophagus should be ameliorated by the help of endoscopic sclerosis.

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4.2.3 *Clonorchis* and *Opisthorchis* Species, Chinese River Fluke (Clonorchiasis, Opisthorchiasis)

1. **Name**: Greek: *klon* = off, branch; *orchis* = testes, testicle. The name *Clonorchis* thus derives from the branching testicles of the worm; *opistho* = behind. The name refers to the two testes lying in the posterior region of the worm.
2. **Geographic distribution/epidemiology**: In Eastern Asia, especially in China, Korea and Japan, about 50 million people are afflicted.
3. **Biology, morphology**: These hermaphrodite worms measure about 10–-20 mm × 3–5 mm (Figs. 4.3 and 4.6); their surface is smooth and shows no hooks. The two highly branched testicles at the posterior end are significant for this species. In the case the front testicle has five, the other one in the back has

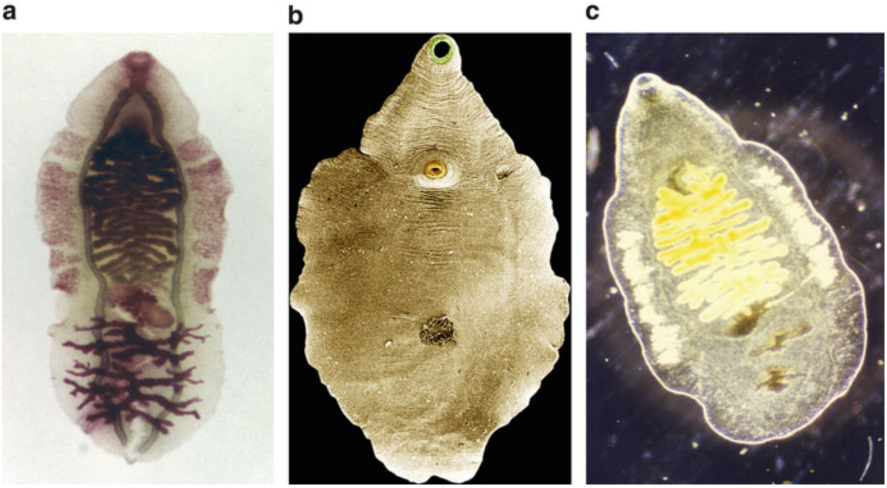

Fig. 4.6 Light micrographs of adult worms of *Clonorchis* (syn. *Opisthorchis*) *sinensis* (**a**, **b**) and *Opisthorchis viverrini*. (**a**) Light micrograph of a coloured stage. (**b**) Scanning electron micrograph. (**c**) Unstained adult worm showing through shining organs

four branches. The infection takes place during consumption of raw or insufficiently cooked fish contaminated with larvae (so-called metacercariae). The fish are non-predatory carps, genus Cyprinidae, originating from sweet water or brackish water. They act as second intermediate hosts for the parasite. Aquatic snails of the genera *Semisulcospira*, *Bulinus* and *Parafossarulus* are the first intermediate hosts. In the intestine of the final host (humans) the larvae hatch. From there they infiltrate the "ductus choledochus" swimming against the currents of gall fluids to the tips of the bile ducts of the liver. Dogs, cats and pigs may act as reserve hosts besides humans.

4. **Symptoms of the disease (Clonorchiasis)**: The severity of the symptoms and the course of the infection depend always on the number of ingested and developed parasites. An infection with 20–200 worms is common in endemic regions. Under these conditions bloating, abdominal pain, swelling of the liver, slight icterus and obstruction of the biliary ducts are induced. In the cases of a massive infection with 1000 up to 20,000 parasites (seen during body obductions) frequently massive bloody diarrhoeas occur as well as ascites, anaemia, different oedema and—even, not often—cirrhosis of the liver. All this may lead to the death of the patient. Abscesses of the liver and cholangiogeneous cancers are further severe symptoms in the cases of strong worm infestations.
5. **Diagnosis**: Microscopical demonstration of the eggs in the feces or in the gall fluid. The operculated ovoid eggs appear brownish and are rather small (35 μm in length). They can be detected by the help of several concentration techniques (Figs. 4.7, 4.8 and 4.18). The PCR method and ultrasonic methods are useful, too. Serodiagnosis (ELISA), however, shows cross reactions with other trematodes.
6. **Pathway of infection**: Orally by ingestion of metacercariae within undercooked or in raw fish (in Korea 1/5 of the human population is infected). Repeated infections are possible due to the lack of an immunization.
7. **Prophylaxis**: Consumption of raw or sufficiently cooked fish (in some areas of China nearly all fish farms are afflicted).
8. **Incubation period**: In cases of high-grade infections: 2 weeks, while low-grade infections may remain symptomless.
9. **Prepatent period**: 2 weeks.
10. **Patency**: 25 years.
11. **Therapy**: The medication of choice is praziquantel (application of 3 × 25 mg/kg bodyweight on a single day).

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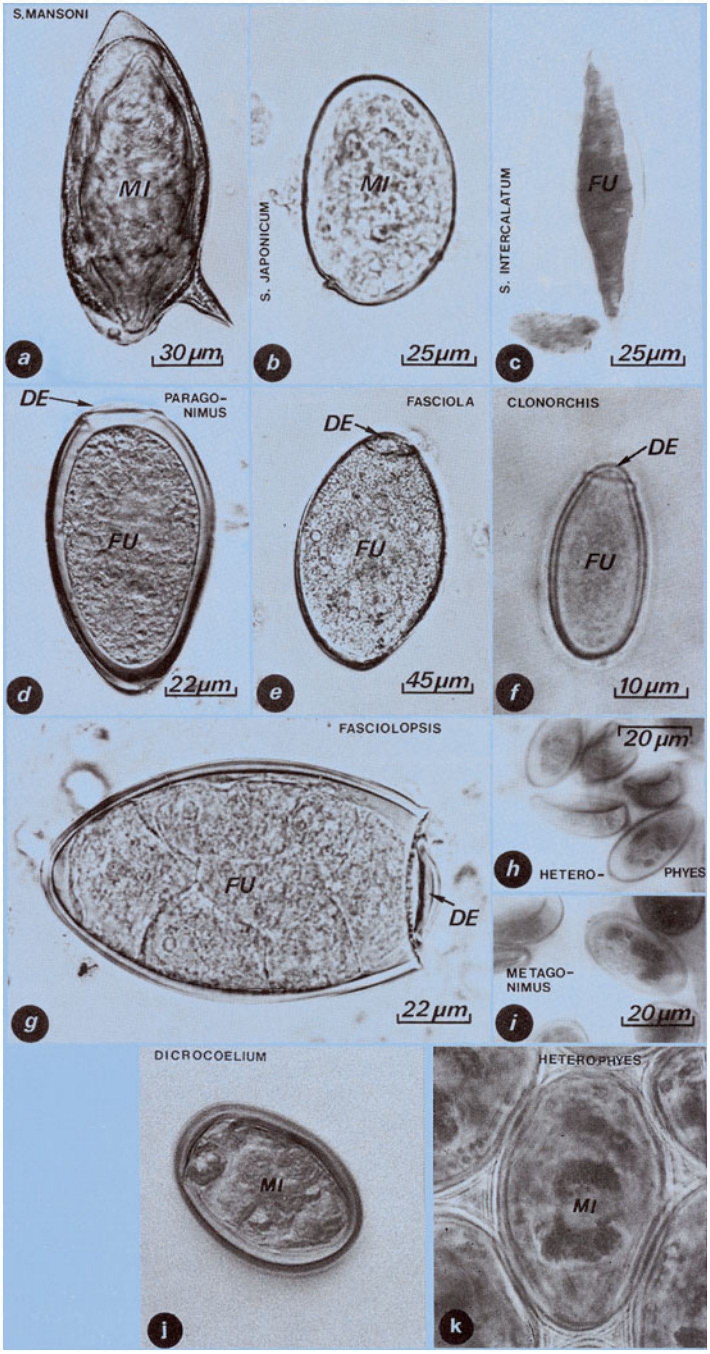
S.MANSONI
MI
a
30 µm
S. JAPONICUM
MI
b
25µm
S. INTERCALATUM
FU
c
25µm
DE
PARAGO-
NIMUS
FU
d
22µm
FASCIOLA
DE
FU
e
45µm
CLONORCHIS
DE
FU
f
10 µm
FASCIOLOPSIS
FU
DE
g
22 µm
20 µm
h
HETERO-
PHYES
METAGO-
NIMUS
i
20 µm
DICROCOELIUM
MI
j
HETEROPHYES
MI
k

Fig. 4.7 Light micrographs of the eggs of important digenetic trematode. *DE* cover (operculum), *FU* developing stage of the larva during development, *MI* miracidium (=typical ciliated larva of trematodes, which may swim by the help of their cilia arranged in rows at their surface)

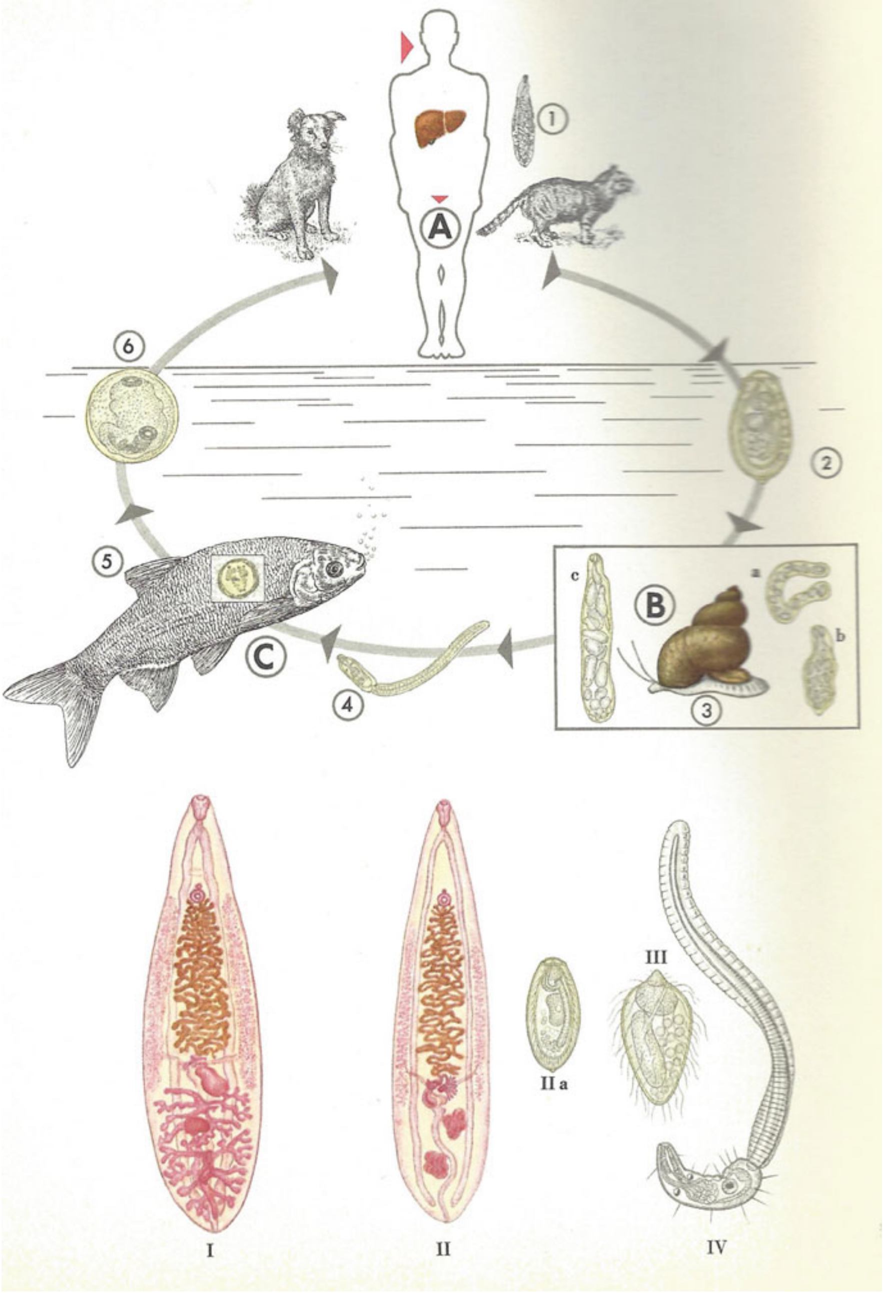

Fig. 4.8 Life cycle of *Clonorchis sinensis* and *Opisthorchis felineus*. (**A**) **Final host**: Man, and also the cat and dog (as well as household and farm animals). (**1**) Sexually mature liver fluke. (**2**) Egg (with miracidium) of *Clonorchis sinensis*. (**B1**) **Intermediate host**: Snails of the genus *Bulimus* (=*Bithynia*) and others. (**3a**) Young sporocyst. (**b**) Mother redia. (**c**) Daughter redia with rudiments of cercariae. (**4**) Cercariae which have become free. (**C2**) **Intermediate host**: Chiefly Cyprinidae. (**5**) Fish with cercariae. (**6**) Metacercariae. (I) *Clonorchis sinensis*.

4.2.3.1 *Opisthorchis viverrini* (Opisthorchiasis)

1. **Name**: Greek: *opisthen* = back; *orchis* = testes. Latin: *viverrinus* = zibet cat-like. Thus, the name reflects the position of the testes inside the worm body and notes the main final host. English: Zibet cat fluke.
2. **Geographic distribution/epidemiology**: In Thailand, focally in Laos, Vietnam, Japan and India about 20 million people are infected. Other hosts are, e.g., zibet cats and other fish-feeding warm-blooded animals.
3. **Biology, morphology**: The adult worms parasitize in the bile ducts (Figs. 4.9 and 4.10), measure 5–9 mm × 0.8–2 mm and can be differentiated from *O. felineus* by their two testes, which show each four lobes, while the egg's shape and size vary only slightly. The infection occurs like in the case of *Clonorchis sinensis* by ingestion of metacercariae inside contaminated meat of fish.
4. **Symptoms of the disease**: See *Clonorchis sinensis*.
5. **Diagnosis**: Microscopical determination of the brownish, operculated eggs, which have a medium size of 27 × 15 μm. Eggs can be isolated from feces by the help of the enrichment methods M.I.F.C. or S.A.F. (Fig. 4.7f) or observed within gall bladder fluid.
6. **Pathway of infection**: Orally while eating raw freshwater fish meat which contains metacercariae. Due to lacking development of immunity, humans, dogs and cats may become repeatedly infected.
7. **Prophylaxis**: Cooking or roasting of fish meat before eating.
8. **Incubation period**: About 14 days.
9. **Prepatent period**: 2–4 weeks.
10. **Patency**: Years, up to 20!
11. **Therapy**: See *Clonorchis sinensis*.

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Fig. 4.8 (continued) (II) *Opisthorchis felineus*. (IIa) Egg of *O. felineus* with miracidium. (III) Free miracidium from a snail. (IV) Cercaria as it typically appears when it is swimming (From Piekarski 1962)

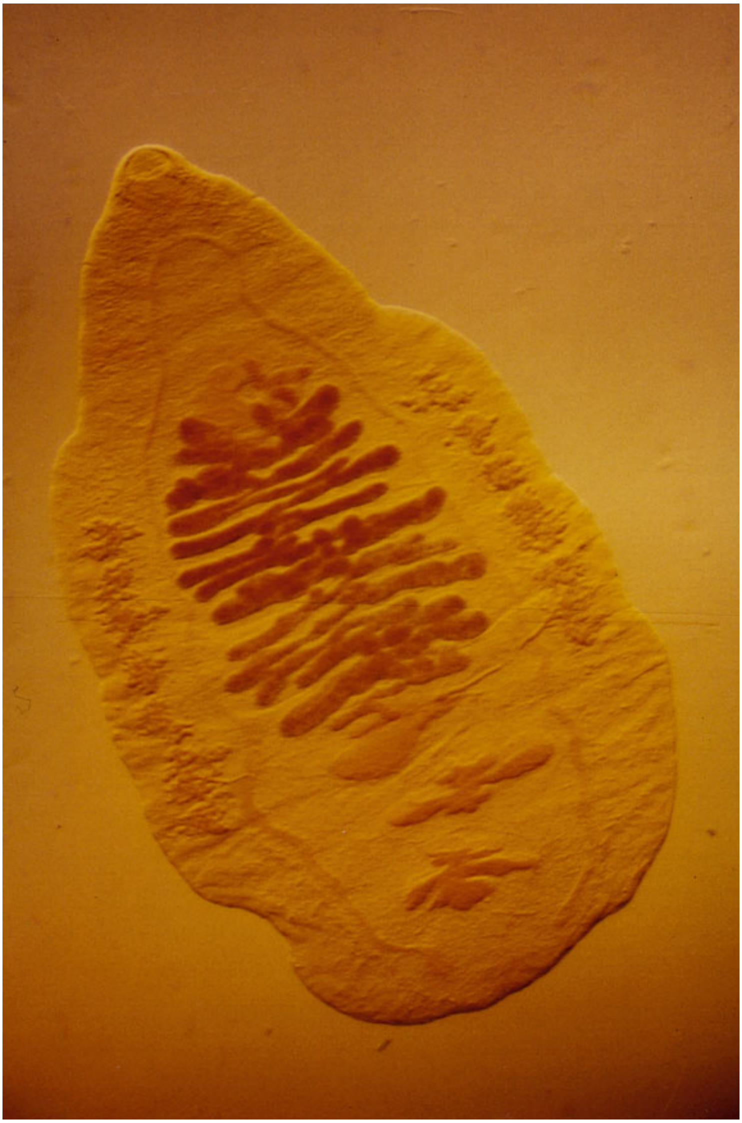

Fig. 4.9 Light micrograph of an unstained living adult worm of *Opisthorchis viverrini*. Note the two lobulated testes in the terminal region. For explanations see Fig. 4.10D–F

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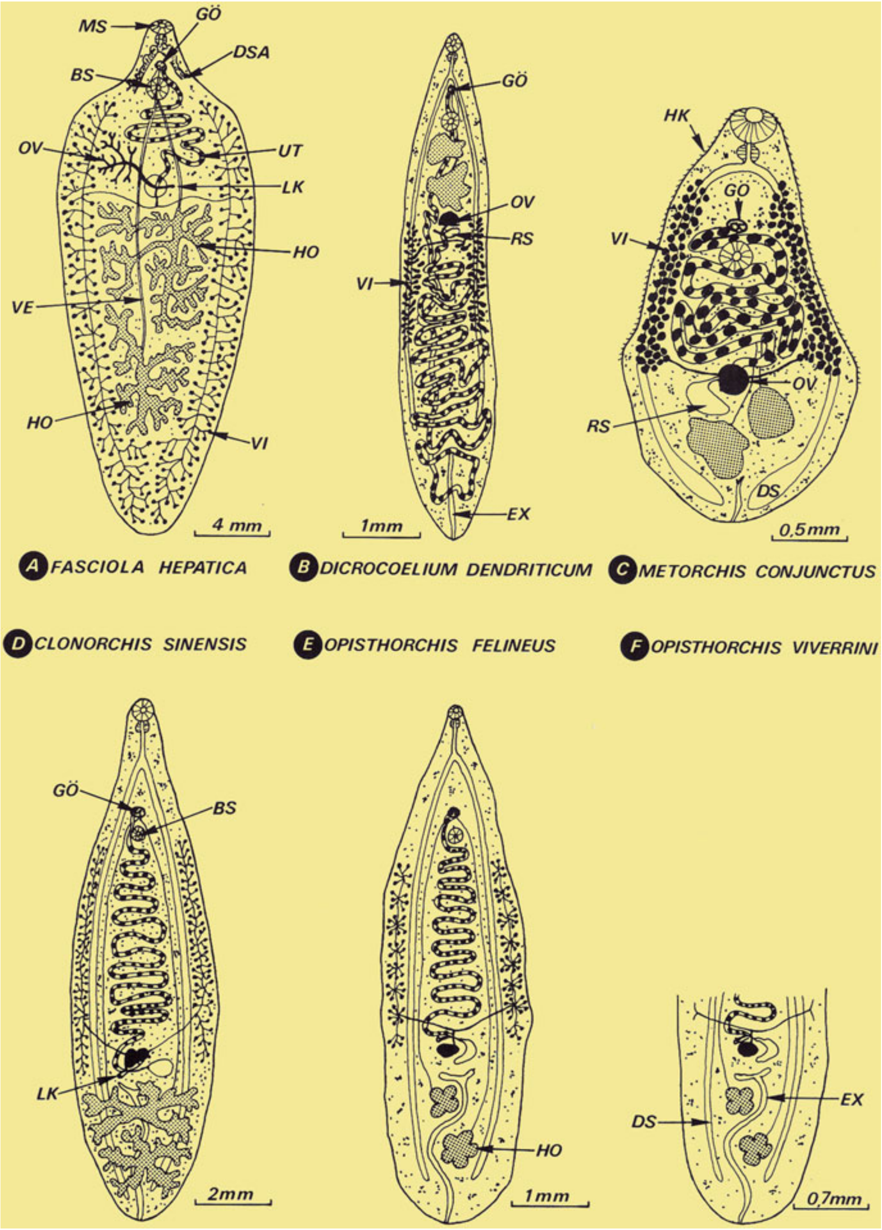
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B DICROCOELIUM DENDRITICUM
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0,5mm
C METORCHIS CONJUNCTUS
D CLONORCHIS SINENSIS
E OPISTHORCHIS FELINEUS
F OPISTHORCHIS VIVERRINI
GÖ
BS
LK
2mm
HO
1mm
EX
DS
0,7mm

Fig. 4.10 (**a**–**f**) Diagrammatic representation of the liver flukes of humans and some related animals. *BS* ventral suckers, *DS* intestinal strands, *DSA* DS shortened in drawing, *EX* excretion channel, *GÖ* genital opening, *HK* hooks in the tegument, *HO* testes, *LK* Laurer's canal, *MS* Buccal sucker, *OV* ovary, *RS* receptaculum seminis, *UT* uterus, *VE* vas deferens, *VI* vitellarium

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4.2.3.2 *Opisthorchis felineus*

1. **Name**: Greek: *opisthen* = back; *orchis* = testes. Latin: *felis* = cat. English: Cat liver fluke.
2. **Geographic distribution/epidemiology**: Northern Europe: focally in countries of Russia, in India, Indochina and Japan, about 10 million people are infected. However, the worm seems to wander also westwards since it was found already in Germany in the Berlin region infecting fish and cats.
3. **Biology, morphology**: The adult dioecious worms live in the bile ducts, measure 8–12 mm in length and 2–2.5 mm in width and are clearly differentiated from *Clonorchis sinensis* by the shape of their testes being less deep invaginated, but show also 4 anterior lobes and five posterior ones (Figs. 4.7b, 4.8 and 4.10). First intermediate hosts are water snails of the genus *Bithynia* (syn. *Bulimus*), while fish species serve as second intermediate hosts. The adult flukes excrete eggs, which measure 30 × 12 μm and appear yellowish and look like those of *Clonorchis sinensis* (Figs. 4.7f and 4.8).
4. **Symptoms of the disease**: See *Clonorchis sinensis*.
5. **Diagnosis**: Eggs (measuring 30 × 12 μm, Figs. 4.7a, f and 4.8)
6. **Pathway of infection**: Oral uptake of metacercariae within raw or undercooked meat of freshwater or brackish water fish.
7. **Prophylaxis**: Heating these fish on at least 55 °C will kill these infectious larvae.
8. **Incubation period**: About one month, symptoms may be low grade in cases of a few worms inside the bile ducts.
9. **Prepatent period**: 2–3 weeks.
10. **Patency**: 15–20 years.
11. **Therapy**: See *Clonorchis sinensis*.

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4.2.4 *Paragonimus* Species (Paragonimiasis)

1. **Name**: Greek: *para* = side by side; *gone* = sexual organ. The two testes are situated side by side in contrast to *Clonorchis sinensis*, where they are situated behind each other. English: Lung fluke.
2. **Geographic distribution/epidemiology**: *P. westermani* (India, Asia), *P. heterotremus* (Thailand), *P. africanus*, *P. uterobilateralis* (Africa), *P. mexicana* (Central and South America), *P. miyazakii* (Japan) and *P. kellicotti* (America, Cuba). Worldwide about 100 million humans are infected.
3. **Biology, morphology**: The dioecious bean-like looking adult worms measure about 7–12 mm in length, 4–7 mm in width and 3–5 mm in diameter (Figs. 4.3 and 4.11). They parasitize mainly inside the lung, where often two are enclosed in a common capsule formed by the host tissue (Fig. 4.11c). Occasionally adult flukes of this species are also found in the tissues of the liver, kidneys, spleen and brain. Adult flukes may reach a lifespan of up to 20 years. They produce golden brownish, operculated eggs, which measure 90 × 60 µm, which contain when excreted (within sputum or feces) only a few cells (Fig. 4.12). In the rare cases of kidney infections, they are also found in the urine. As soon as these worms have reached water, they develop inside a ciliated miracidium larva, which penetrates after hatching from the egg into different water snails (e.g. specimens of the genera *Semisulcospira*, *Melania*, *Hia*, *Thiara*, *Brotia*, *Pomatiopsis*), which thus become the **first intermediate host**. After a developing phase within sporocysts so-called cercariae leave the snails and enter crabs, which become **second intermediate hosts**. Inside their tissues, the infectious stages (metacercariae) are formed. The infection of humans and several animal hosts occurs during ingestion of contaminated raw meat of such crabs. In the intestine of final hosts (humans, animals), the young flukes penetrate the intestinal wall and migrate via peritoneal cavity and diaphragm into the lungs (but also in other organs), where they become adults being situated in cyst-like structures (often as pairs).
4. **Symptoms of the disease**: After a rather long incubation period of about 3–6 months, the following symptoms of the disease may occur (depending on the site of the infected organ):
   (a) **Lung paragonimiasis**:

   Tuberculosis-like haemoptysis, bronchitis and breast pain, fever and breathing problems; sputum contains a large number of eosinophilic leucocytes and so-called Charcot–Leyden crystal-like bodies. In X-ray examinations, the pictures are very similar to those of tuberculosis showing also infiltrations of cells and formations of caverns after degeneration or abscesses. Furthermore, bronchial ectasia and pleural effusions may occur. **Differential diagnosis** to tuberculosis is based on the presence of an eosinophilia within the bloody or brownish excreted sputum and the occurrence of the typical *Paragonimus* eggs therein (Fig. 4.12). If the

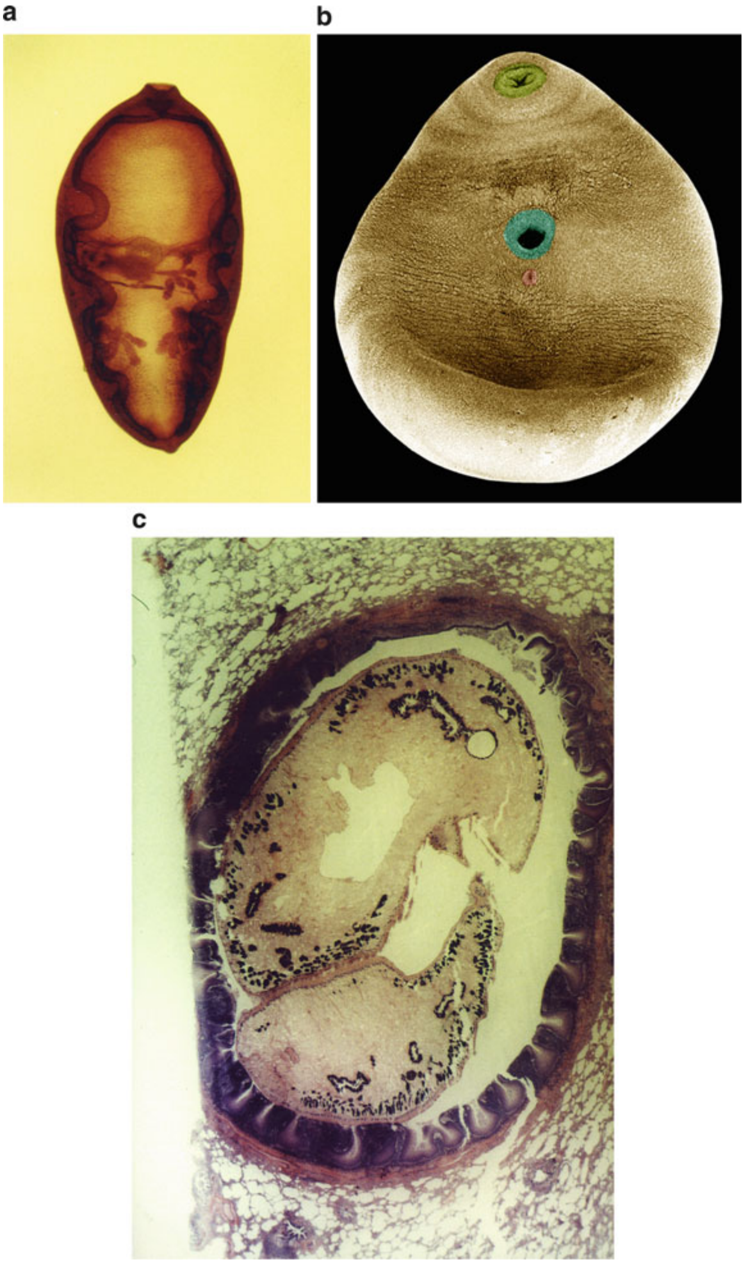

Fig. 4.11 *Paragonimus westermani*. (**a**) Colorated adult stage. (**b**) Scanning electron micrograph of the ventral side of an adult stage showing its smooth surface and the oral and ventral suckers (**c**) Section through a cyst (in a patient's lung) containing two adult specimens of *P. westermani*

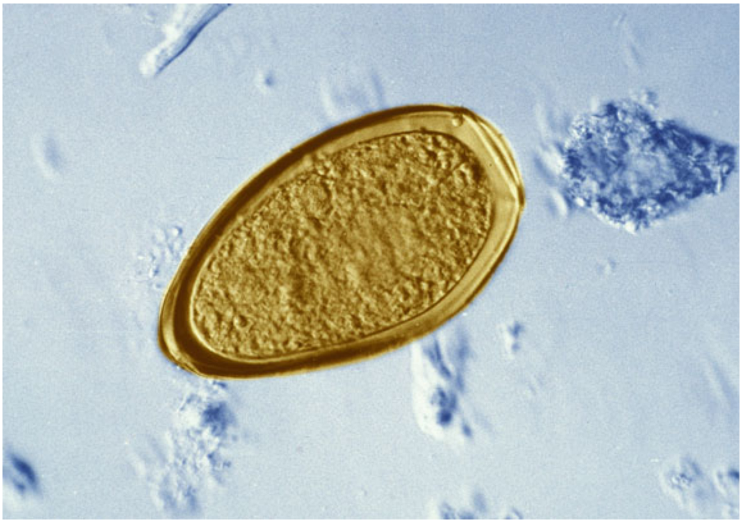

Fig. 4.12 *Paragonimus westermani*. Light micrograph of a freshly excreted non-embryonated egg

sputum is swallowed, these eggs then occur (often in very large numbers) inside the feces.

(b) **Abdominal paragonimiasis**:

As a follow-up of the permanent tissue irritations due to the presence of adult worms and due to their excreted eggs unspecific pain occurs in various infested organs, which also may lose their functions. Very often typical lymph node swellings occur.

(c) **Cerebral paragonimiasis**:

Typical symptoms are headache, fever, epileptic attacks and neurologic dysfunctions, which are similar to reactions on tumour formations or typical vascular dysfunctions. In the case of HIV patients other symptoms like cerebral toxoplasmosis, lymphomas, tuberculomas and progressive leuco-encephalopathy have to be excluded. During examination of the liquor, increase of proteins and eosinophilia is especially prominent. The latter is not present in HIV patients, while prominent in cases of cysticercosis (e.g. due to *Taenia solium* infections). Since in endemic regions of paragonimiasis mostly sophisticated diagnosis is not possible, cerebral paragonimiasis is mostly only diagnosed during *post-mortem* examinations.

5. **Diagnosis**: The eggs of the *Paragonimus* species can be found during light microscopical examination of probes of the sputum and the feces (S.A.F., M.I. F.C.), but also in pleural infiltrations, urine or lung biopsies. Probes of sputum can be examined for eggs as follows:

   (1) Sputum is mixed 1–2 ml 5 % NaOH

(2) Filled up with aqua dest
(3) Centrifuged for 5 min at 1500 g
(4) Examined by light microscopical examination

Serological tests (e.g. ELISA) show high sensitivity and specificity. The cases of cerebral infections may be diagnosed by the help of antibodies within the fluid. X-ray investigations and computer tomography show especially adult worms in cysts, which may reach diameters of up to 4 cm. Even repeated ingestion of *Paragonimus* larvae does not introduce immunity.

6. **Pathway of infection**: Oral uptake of infected raw or undercooked meat crabs, e.g., of the genus *Eriocheir* (in case of *Paragonimus westermani*) or *Cambarus* (in the case of *P. kellicotti*).
7. **Prophylaxis**: Avoidance to eat raw or undercooked meat of freshwater crabs.
8. **Incubation period**: 9–12 weeks.
9. **Prepatent period**: 10–12 weeks.
10. **Patency**: Up to 20 years.
11. **Therapy**: Drug of choice is praziquantel (3 × 25 mg/kg bodyweight daily for 2 days).

Further Reading

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Kodama M et al (2014) Cutaneous paragonimiasis due to triploid *Paragonimus westermani* presenting as a non-migratory subcutaneous nodule: a case report. J Med Case Rep 8:346–350

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4.2.5 *Fasciolopsis buski* (Fasciolopsiasis)

1. **Name**: Latin: *fasciola* = little tape. Greek: *opsis* = appearance. English: Giant intestinal fluke.
2. **Geographic distribution/epidemiology**: This worm occurs especially in India, Bangladesh, China, East Asia, Borneo, Sumatra and Taiwan; about

40 million people are infected. In Europe also many cases occur due to import and eating of water chestnuts (*Trapa natans*) at which metacercariae are (invisible) attached.

3. **Biology, morphology**: *F. buski* is the largest trematode occurring in the intestine of humans reaching about 7–8 cm in length, 2–3 cm width and a thickness of about 2–3 mm (Figs. 4.3, 4.13 and 4.14). The dioecious adult flukes become attached by their two suckers at the surface of the upper duodenum. Their excreted eggs have a size of 130–140 μm × 80 μm and cannot be significantly differentiated from those of *Fasciola hepatica* (Figs. 4.7e, g and 4.8). The non-embryonated eggs are excreted within the feces. After an inner development the miracidium larva hatches from the egg (Fig. 4.3) and enters finally the first intermediate host (water snails of the genera *Planorbis*, *Segmentina*, *Hippeutis*, *Gyraulus* species, etc.), wherein an asexual reproduction is proceeded via sporocysts and finally rediae which give rise to tailed cercariae, which swim around and attach themselves at water plants (especially in Asia at the fruits of the so-called water nut or water caltrop (*Trapa natans*) and transform themselves to encysted metacercariae (Figs. 4.3 and 4.14). Infection of humans (and some plant-feeding animals) occurs by uptake of such contaminated water nuts. The worm stages survive even transport to Europe, where people (e.g. in Düsseldorf, Germany) had been infected. However, in endemic regions cattle and pigs represent important reservoir hosts. In addition also cats, dogs and rabbits were found to be infected at high rates.
4. **Symptoms of the disease (Fasciolopsiasis)**: Even if many worms occur inside infected humans, symptoms may be not noted immediately. However, after a rather long incubation period of 1–3 months symptoms like nausea, vomiting (inclusive discharge of worms via the oral route), diarrhoeas or winds may occur. In cases, which occur mainly in endemic regions, infections by large numbers of these worms may induce anaemia, weakness, loss of weight, oedemas and/or ascites. Especially very young children may die, if severe infections are not recognized at an early stage of the infection.
5. **Diagnosis**: The rather large operculated eggs of *Fasciolopsis buski* (Fig. 4.18) measure 130–140 μm × 80–85 μm and are characterized by a large operculum (cover), which is lifted during the process of hatching of the typical miracidium larva. The development of the miracidium inside the egg shell starts after the egg has reached water. The differentiation between eggs of the genus *Fasciola hepatica*, *Echinostoma* sp. and those of *F. buski* is difficult when checking them just by light microscopy. In cases of high-grade infections occasionally motile adult worms were found in vomited material or in rather fluid feces.
6. **Pathway of infection**: Oral by ingestion of metacercariae being attached at water plants and/or at their fruits (e.g. at bamboo, lotus, water chestnuts or water caltrop). Due to a lack of immunization, repeated infections may occur thus increasing the worm load in the human intestine.
7. **Prophylaxis**: Avoidance of ingestion of uncooked water plants.
8. **Incubation period**: 1–3 months.
9. **Prepatent period**: 2–3 months.

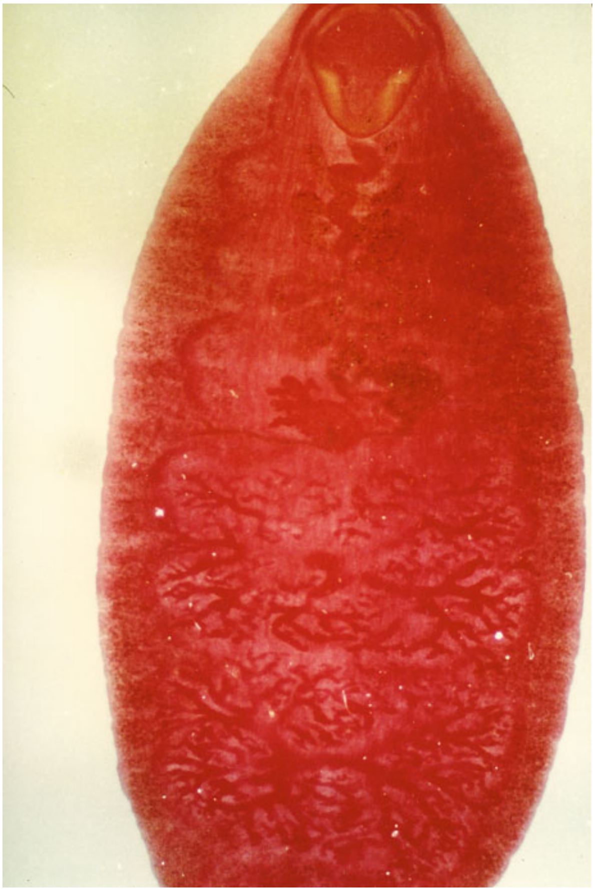

Fig. 4.13 Light micrograph of a *red*-stained adult *Fasciolopsis buski* worm, which has a rather thick tegumental layer so that the organs are only poorly seen except for the two intensively branched testes inside the posterior portion of the body

10. **Patency**: About 1 year.
11. **Therapy**: Drug of choice is praziquantel (1 × 15 mg/kg bodyweight). Niclosamide and tetrachloroethylene are also effective, but not registered in many countries.

Further Reading

Biswal DK et al (2013) An integrated pipeline for next generation sequencing and annotation of the complete mitochondrial genome of *Fasciolopsis buski*. Peer J. doi:10.7717/peerj.207

Fiamma M et al (2015) *Fasciolopsis buski* infection in a Vietnamese pregnant women with systemic lupus erythematosus. J Infect Dev Ctries 9:670–673

Prasad PK et al (2011) PCR-based molecular characterization of *Paragonimus westermani*, *Fasciolopsis buski* and *Fasciola gigantica*. Bioinformation 6:64–68

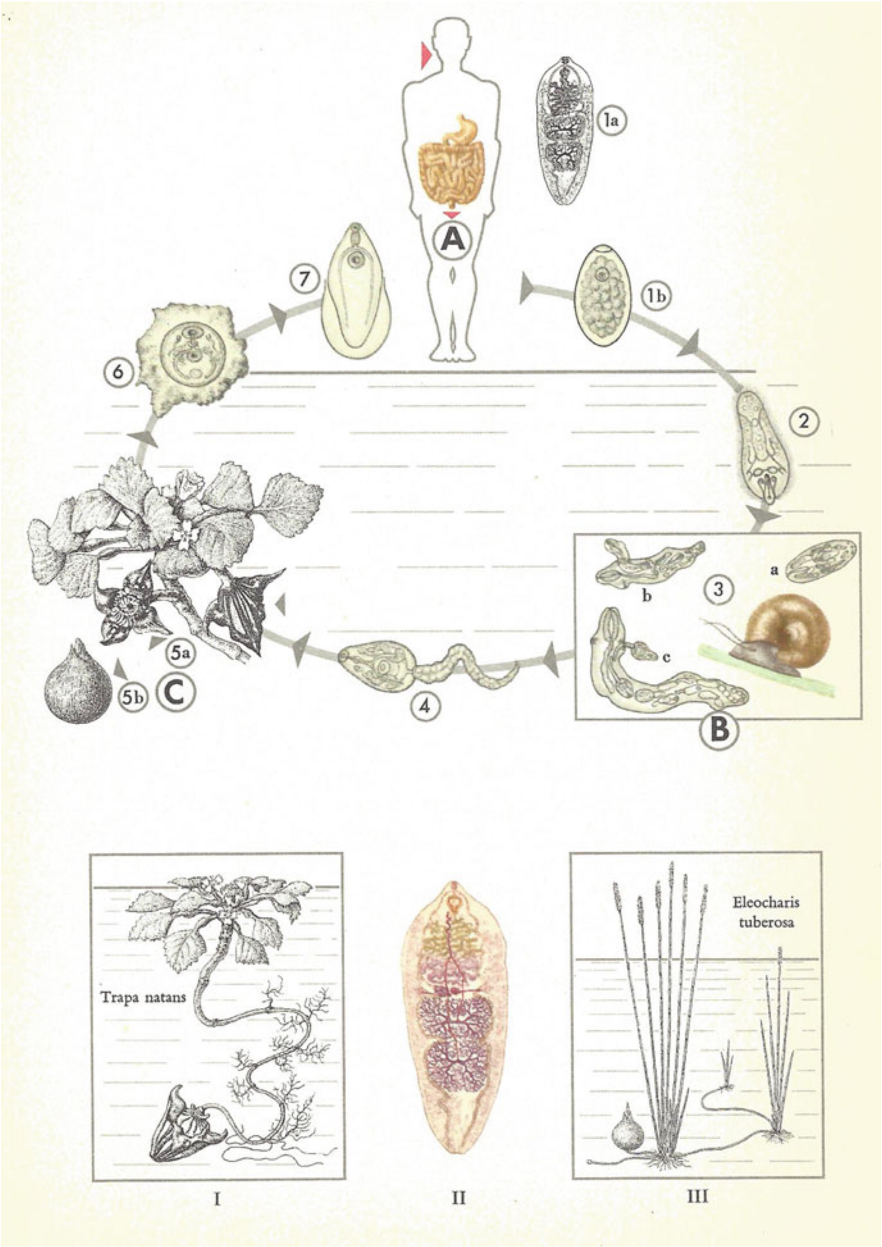

Fig. 4.14 Diagrammatic representation of the life cycle and life cycle stages of *F. buski* (according to Piekarski 1962). (**A**) **Final host man**. (**1a**) Adult worm, (**1b**) Egg containing developing cells, (**2**) Hatched miracidium larva entering water snails. (**B**) **Development inside snail host**. (**3a**, **b**, **c**) Development inside snail host. (**4**) Hatched cercaria in water seeking for a plant to attach thereon. (**C**) **Development on plants**. (**5a**) Fruits of the water caltrop (*Trapa natans*) belonging to the water chestnuts. (**5b**) Bulb of water chestnut *Eleocharis tuberosa*. (**6**) Metacercaria from a water caltrop plant. (**7**) Young motile worms (occurring in the intestine of

Yamaguti S (1958) Systema helminthicum, vol 1. The digenetic trematodes of vertebrates. Interscience, New York

4.2.6 *Fasciola hepatica* (Fascioliasis)

1. **Name**: Latin: *fasciola* = small = tape; *hepar* = liver; English: Common giant liver fluke.
2. **Geographic distribution/epidemiology**: Worldwide, due to the peculiar way of infection only a few humans (especially mostly children) are infected (~several thousand worldwide, but very common among ruminants).
3. **Biology, morphology**: The dioecious adult worms measure in general 2–-5 cm × 4–14 mm; however, they may reach in some cases up to 7 cm (Figs. 4.3 and 4.15a, b). The adults are in general found in the bile ducts of ruminants, but occasionally also in those of humans. When unstained the large spreaded intestinal system is visible by the help of its dark/blackish appearing contents. Coloured specimens (Fig. 4.15a) show that this intestinal practically fills the whole body while the sexual system is concentrated at the apical pole. The surface of the adult worms is densely covered by large scales, which help that they may stay inside the bile ducts (channel system) of humans (Fig. 4.15b). The operculated eggs (Fig. 4.18) are excreted within the feces in a multicell stage and formation of the miracidium larva starts as soon as the egg has reached water. At this stage, the eggs reach a size of 130–190 μm × 63–90- μm, appear yellowish up to light brown and possess a relatively tiny operculum, which is thrown off when the ready-to-leave miracidium larva is ready to hatch from the egg interior. The development of the larva inside the egg takes 1–2 weeks depending on the water temperature. Free swimming larvae look like unicellular ciliates, but are multicellular and contain clusters of undifferentiated cells, which later develop asexually into sporocysts that later produce and set free the rediae. Inside the rediae the cercariae are produced, which attach themselves at water plants. There they excrete a covering layer and thus become so-called metacercariae, which are the infectious stage for the final hosts. As soon as such final hosts have ingested such metacercariae, the included larva hatches, penetrates the intestinal wall and finally enters the liver after passing the body cavity. However, several young worms also enter other organs and thus adult worms are occasionally found in organs such as spleen and lung and enter even into eyes and brain.
4. **Symptoms of the disease (Fascioliasis)**: After an incubation period of about 2–3 weeks, the wandering larvae induce symptoms like liver inflammations, fever of about 38 °C, loss of appetite, weakness and enlargement of the liver. Ongoing infections show symptoms like dyspepsia, liver pain, strong

Fig. 4.14 (continued) humans). (**I**) *Trapa natans* (water caltrop) in water. (**II**) Sexually mature fluke. (**III**) *Eleocharis tuberosa* (Chinese water chestnut)

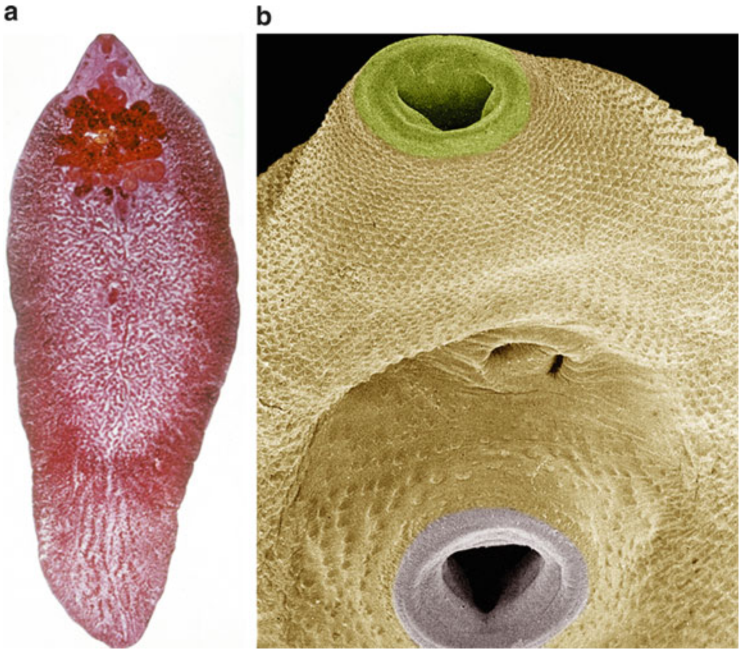

Fig. 4.15 *Fasciola hepatica*. (**a**) Light micrograph of an adult worm coloured by *carmine red*. (**b**) Scanning micrograph showing the oral and ventral sucker, the closely attached openings of the female and male system and the typical hooks in the tegument

enlargement and calcification of the bile ducts, ascites, pleural and pericardial fluid infiltrations and cirrhotic symptoms. The blood picture often shows signs of anaemia with a significant eosinophilia.

5. **Diagnosis**: The large 130–160 μm × 60–90 μm sized operculated eggs are mostly rarely seen in the large amount of fresh feces. However, the use of enrichment methods (e.g. M.I.F., S.A.F. or sedimentation) allows effective diagnose in a rather short time. In the case of low-grade infection the eggs can be easily observed in centrifuged gall fluid. Eggs of adult worms sticking in liver parenchyma can mostly be only seen in biopsy material or if computer tomography tests were done. Serologic tests (e.g. ELISA) are helpful during the prepatent period or if worms stick within the liver parenchyma.
6. **Pathway of infection**: Oral during ingestion of metacercariae being attached at fruits or leafs of water plants. Since infections do not lead to immunity, repeated infections are possible.
7. **Prophylaxis**: Washing and cooking of water plants in endemic regions.
8. **Incubation period**: 3–12 weeks.
9. **Prepatent period**: 3–4 months.
10. **Patency**: 1–20 years.
11. **Therapy**: Until now only triclabendazole (1 × 10 mg/kg bodyweight) showed full efficacy. Bithionol, niclofolan and emetine turned out to be less effective

and induce often side effects. Albendazole and praziquantel were not effective, when the dose was given at once. However, if the daily dose was divided into six applications and if this treatment was repeated for 3–7 days the stages sticking in the liver were killed, too.

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Bui TD et al (2015) Current status of fasciolosis in Vietnam. J Helminthol. doi:10.1017/SSS0022149X15000929

Cwiklinski K et al (2015) The *Fasciola hepatica* genome. Genome Biol. doi:10.1186/s13059-015-0632-2

Fernandez V et al (2015) A single amino acid substitution in isozyme GST mu in triclabendazole resistant *Fasciola hepatica* can influence antihelminthic resistance. Exp Parasitol 159:274–279

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4.2.7 *Dicrocoelium dendriticum* (syn. *lanceolatum*) (Dicrocoeliasis)

1. **Name**: Greek: *dikroos* = bifurcated; *koila* = abdominal cavity. English: Small liver fluke, lancet fluke.
2. **Geographic distribution/epidemiology**: Worldwide in regions with lime-rich soils; especially common in North Africa, Siberia, South America; however, rather rare in humans, but mainly in sheep, cattle.
3. **Biology, morphology**: The dioecious adults of this species reach a length of 5–12 mm and a width of 1–2 mm. Their surface is smooth and does not contain scales (Fig. 4.16b). They live mainly in the bile ducts of ruminants and are only rarely found in humans (Figs. 4.10 and 4.16), since the infection occurs by oral uptake of so-called metacercariae which occur in the second intermediate host (ants). Infected ants bite in the evening into leafs of plants, stay there overnight and thus may become ingested next morning together with such plants. Having reached the duodenum the young worms hatch from the ant's tissue and enter the liver via the ductus choledochus.
4. **Symptoms of the disease (Dicrocoeliasis)**: The main symptoms are rather non-specific and are characterized by pain in the upper belly region induced by a swelling of the liver in cases of infection by numerous flukes. In cases of low-grade infection, symptoms, however, remain mostly rather unspecific and are not painful. This is explained by the fact that the young flukes enter the liver

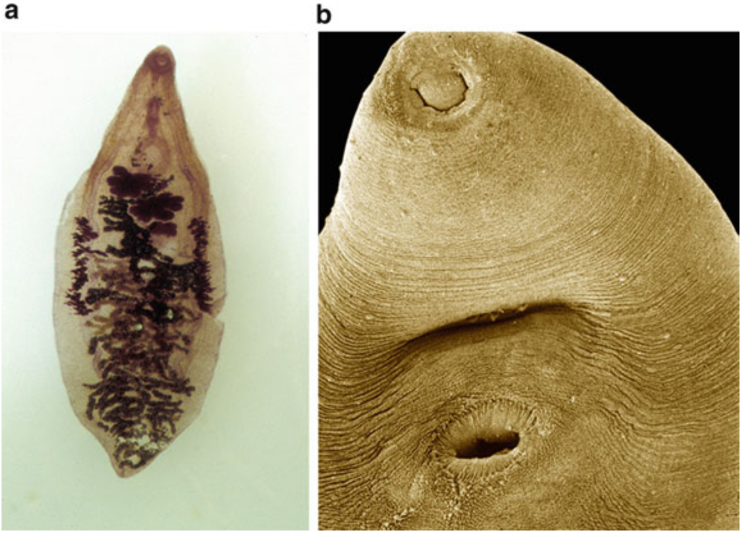

Fig. 4.16 *Dicrocoelium dendriticum*. (**a**) Light micrograph of a coloured adult. (**b**) Scanning electron micrograph of the anterior end of an adult fluke, which has a smooth surface. The two genital openings are hidden below the fold between the upper mouth sucker and the lower ventral sucker

via the ductus choledochus and not by penetration of the liver from its outside as it is the case in *Fasciola hepatica*.

5. **Diagnosis**: Microscopically determination of the typical brownish rather tiny (18–45 μm × 20 μm) eggs, which appear in the feces and can be obtained by use of concentration methods (M.I.F., S.A.F.). If infected livers of animals have been eaten, an infection may be feigned, but these eggs just pass the human intestine.
6. **Pathway of infection**: Oral by uptake of metacercariae (350 μm × 25 μm) inside ants or parts of them being attached at salad or other plants.
7. **Prophylaxis**: Intense cleaning of salad and other plants before eating. Avoidance of mouth contacts with grass leafs from cow meadows.
8. **Incubation period**: 2–4 weeks up to several months.
9. **Prepatent period**: 7–8 weeks.
10. **Patency**: Years.
11. **Therapy**: See *Clonorchis* (Sect. 4.2.3.1).

Further Reading

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Cabeza-Barrera I et al (2011) *Dicrocoelium dendriticum* an emerging spurious infection. Ann Trop Med Parasitol 105:403–406

Sandoval H et al (2013) A tool for diagnosis of *Dicrocoelium dendriticum* infection. Parasitol Res 112:1589–1595

Vokral I et al (2012) The inability of tapeworm *Hymenolepis diminuta* and fluke *Dicrocoelium dendriticum* to metabolize praziquantel. Vet Parasitol 185:168–174

4.2.8 *Heterophyes* Species (Heterophyiasis)

1. **Name**: Greek: *heteros* = different; *phyes* = shape.
2. **Geographic distribution/epidemiology**: East Asia, Egypt, South Europe; about 30–40 million humans are infected.
3. **Biology, morphology**: The adult stages appear pear shaped and measure 2 × 0.4 mm and thus are rather small. They occur in the small intestine and caeca of humans, dogs, cats and other animals in case they ingest infected fish meat. *H. heterophyes* is characterized by a muscular bulge, which surrounds the genital openings being situated below the ventral suckers. The slightly brownish, operculated, embryonated (when excreted) eggs measure 25–30 μm by 15–17 μm and are set free within the host's feces. If they reach freshwater, the miracidium larva hatches and enters water snails as first intermediate host. Second intermediate hosts are brackish water fish, which contain the infectious metacercariae. The infection of humans occurs by oral uptake of these metacercariae in raw fish meat.

   A similar life cycle exists in Thailand in the case of the species *Stellantchasmus falcatus*, which reach a size of 0.5 × 0.2 mm and have mainly dogs, cats and fish eating birds as final hosts. Snails of the genus *Thiara* are first intermediate hosts and mugilid fish act as second intermediate hosts.
4. **Symptoms of the disease**: In cases of massive infections, strong diarrhoeas occur starting after an incubation period of 2–3 weeks. In cases of the penetration of the intestinal wall, eggs and occasionally also adult worms reach the heart, lung or brain, which may lead to the death of these infected persons.
5. **Diagnosis**: Microscopically determination of the very small eggs (Fig. 4.18) by the help of enrichment methods (M.I.F., S.A.F.). An exact species determination is difficult, but not needed with respect to the fact that therapy is identical.
6. **Pathway of infection**: Oral by ingestion of raw or undercooked, but metacercariae containing fish meat.
7. **Prophylaxis**: Fish should be sufficiently heated before eating.
8. **Incubation period**: Depending on the amount of ingested metacercariae, first symptoms occur after about 1–3 weeks. In cases of low-grade infections even no symptoms may be initiated.
9. **Prepatent period**: 1–2 weeks.
10. **Patency**: 2–6 months.
11. **Therapy**: See *Clonorchis sinensis*.

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Ashour DS et al (2014) Insights into regulatory molecules of intestinal epithelial cell turnover during experimental infection with *Heterophyes heterophyes*. Exp Parasitol 143:45–54

Chontananarth T et al (2014) Molecular phylogeny of trematodes in the family Heterophyidae. Asian Pac J Trop Med 214:446–450

Elshazly AM et al (2008) Comparison of three immunodiagnostic tests for experimental *Heterophyes heterophyes* infection in dogs. Vet Parasitol 151:196–202

Thaenkham U et al (2012) Families Opisthorchiidae and Heterophyidae: are they distinct? Parasitol Int 61:90–93

4.2.9 *Metagonimus yokogawai* and Related Species (Metagonimiasis)

1. **Name**: Greek: *meta* = behind, later; *gone* = sexual organ, reproduction. Muneo Yokogawa (1918–1995) = famous Chinese scientist (later President of the Japanese Society of Parasitology). He described in Japan (Chiba) many new trematodes. English: spiny intestinal fluke.
2. **Geographic distribution/epidemiology**: Mainly in East Asia, but also focally in Romania, Spain, Russia, Israel; about 5–10 million humans are infected.
3. **Biology, morphology**: These flukes are rather tiny measuring about 1-–2.5 mm × 0.4–0.7 mm. The surface of their tegument is covered with fine spikes. The ventral sucker is not centrally situated but laterally displaced. The adult worms can be found in the small intestine of fish-feeding mammals (inclusive humans) but also in birds (Fig. 4.3). The small sized, operculated eggs (measuring 27 × 16 μm) contain already a miracidium larva as soon as they are excreted within the feces of their hosts. In water the miracidium larva hatches from the egg and enters water snails of the genera *Melania* and *Sulcospira*. Other features of the life cycle are very similar to those of *Clonorchis sinensis*.
4. **Symptoms of the disease**: After an unknown incubation period and in cases of mass infections (thousands of the tiny adults), severe diarrhoeas had been described.
5. **Diagnosis**: Microscopically determination of the operculated, tiny, embryonated eggs (Fig. 4.18) within feces after use of concentration methods (S.A.F., M.I.F.). Exact species determination based just on egg morphology is not possible.
6. **Pathway of infection**: Oral uptake of uncooked fish meat containing metacercariae.
7. **Prophylaxis**: Fish meat should be cooked or grilled.
8. **Incubation period**: 1–3 weeks depending on the amount of ingested metacercariae.
9. **Prepatent period**: 1–2 weeks.
10. **Patency**: 6–10 months.

11. **Therapy**: Drug of choice is praziquantel, which should be used by application of a single dose of 20 mg/kg body weight. Niclosamide and tetrachloroethylene are also efficient.

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Shimazu T, Kino H (2015) *Metagonimus yokogawai*: from discovery to designation of a neotype. Korean J Parasitol 53:627–639

4.2.10 *Echinostoma* Species (Echinostomiasis)

1. **Name**: Greek: *echinos* = spines, hedgehog. Latin: *stoma* = round, opening; *canis* = *dog*. English: spiny collar fluke.
2. **Geographic distribution/epidemiology**: In Southeast Asia, Japan and India, several hundred thousands of humans are infected (mostly probably without knowledge).
3. **Biology, morphology**: *E. ilocanum* (Fig. 4.17) reaches a size of 7 × 1.5 mm and parasitizes inside the whole small intestine. This hermaphroditic fluke is characterized by an anterior collar bearing 49–41 thorns (Fig. 4.17). Due to the fact that these flukes suck blood at the finally destructed intestinal wall, they may appear slightly or even dense red. Their eggs contain only masses of undifferentiated cells when discharged within the feces. They are ovoid, possess an operculum, appear yellow brownish, are operculated and measure about 90–115 µm × 60–70 µm (Fig. 4.18). These eggs are excreted within the feces and—in case they reach water—they develop inside a typical miracidium larva, which hatches after temperature-dependent periods and enters the first intermediate host (water snails belonging to the genera *Gyraulus* or *Hippeutis*). As second intermediate hosts serve again water snails (genera *Pila*, *Lymnaea* or *Viviparus*) and occasionally also mussels (*Corbicula* species). The infections of the final hosts (humans, dogs, birds) occur by oral uptake of metacercariae within raw snails or mussels. After the metacercariae have hatched inside the host's intestine from their cover, these young worm stages become attached at the surface of the intestine in the region of the jejunum.
4. **Symptoms of the disease**: In the case that many worms occur inside the intestine, the intestinal wall may become severely damaged by the numerous hooks at the apical pole of these flukes (Fig. 4.17). This initiates severe diarrhoeas leading to significant dehydration and body pain. In many cases, patients reported signs of an intoxication, strong headache and signs of

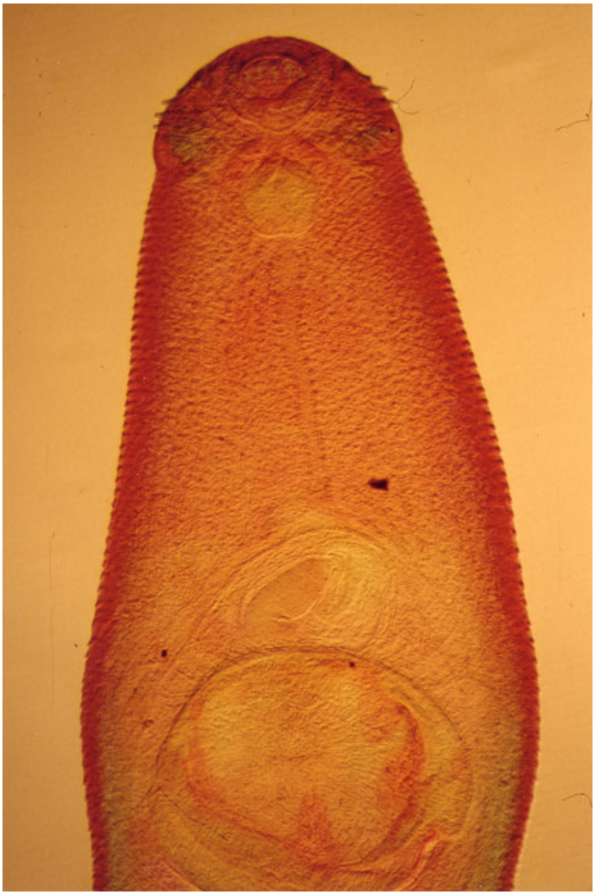

Fig. 4.17 Light micrograph of the anterior pole of an adult worm of the species *Echinostoma ilocanum*. Note the hooks of the anterior pole around the mouth sucker and the large ventral sucker

anaemia, which in the first phase of the infection also may initiate a significant eosinophilia.

5. **Diagnosis**: Microscopically determination of the eggs, which appear similar to those of *Fasciola hepatica* and *Fasciolopsis buski* (Fig. 4.18). Due to the large size of the eggs, the so-called sedimentation method is very sensitive, so that even low numbers of eggs can be easily detected.
6. **Pathway of infection**: Humans and other hosts become infected when ingesting raw mussels or snails being contaminated with metacercariae. However, the metacercariae are rather small (0.2 mm) and thus can by the help of the naked eye hardly be seen in the meat of the intermediate hosts and thus are easily missed during inspections.
7. **Prophylaxis**: Cooking or baking of mussels and snails before eating.
8. **Incubation period**: 1–3 weeks.
9. **Prepatent period**: 2–3 weeks.
10. **Patency**: 6–12 months.
11. **Therapy**: See *Fasciolopsis buski* (Sect. 4.2.5).

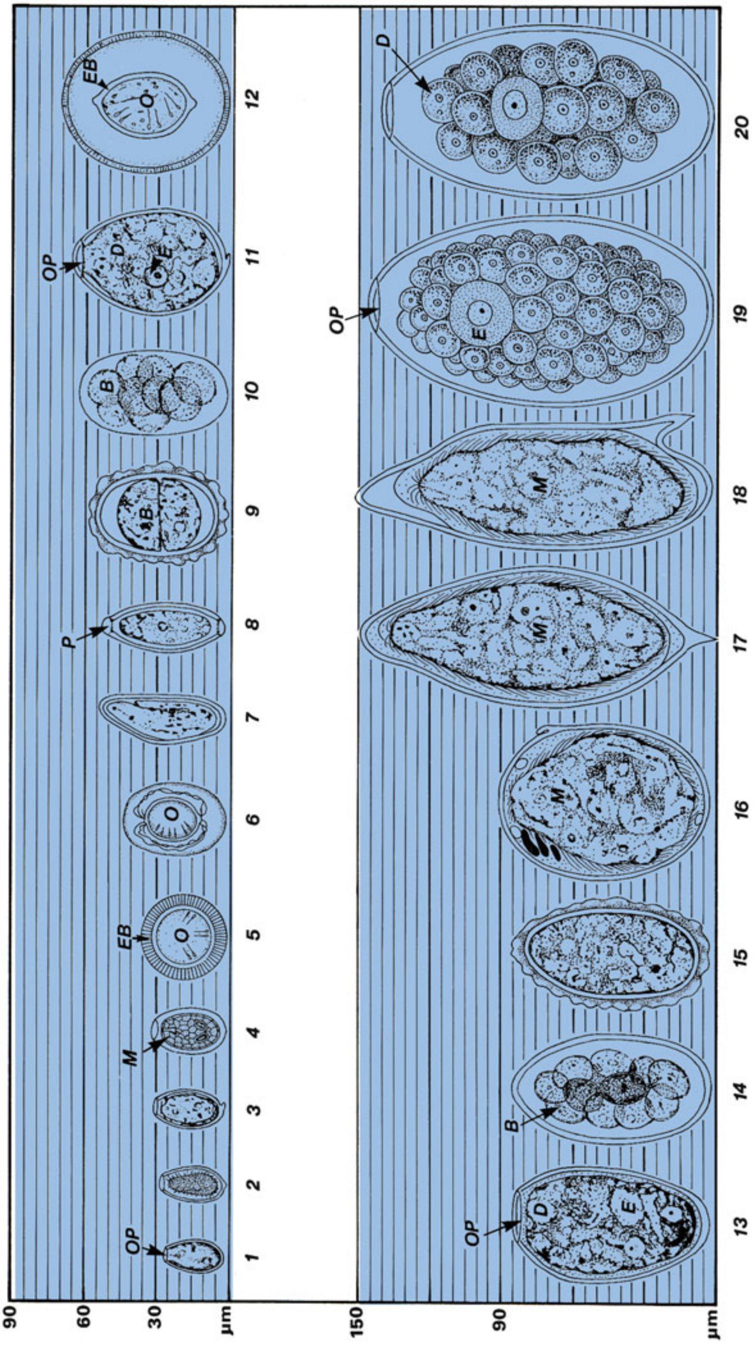
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Fig. 4.18 Diagrammatic representation of the size and appearance of eggs of 22 important parasitic worms of humans shown in comparison according to data published by WHO. (**1**) *Metagonimus yokogawai*; (**2**) *Heterophyes heterophyes*; (**3**) *Clonorchis sinensis*; (**4**) *Dicrocoelium dendriticum*; (**5**) *Taenia* species; (**6**) *Vampirolepis* (syn. *Hymenolepis*) *nana*; (**7**) *Enterobius*

Further Reading

Cortes A et al (2015) Differential alterations in the small intestine epithelial cell turnover during acute and chronic infection with *Echinostoma caproni*. Parasites Vectors. doi:10.1186/s13071-015-0948-S

Georgieva S et al (2014) *Echinostoma revolutum* species complex revisited. Parasite Vectors 7:520

O'Sullivan C et al (2013) Metabolic profiling of *Echinostoma caproni*. Acta Parasitol 58:1–5

Zimmermann MR et al (2014) Differences in snail ecology lead to infection pattern variation of *Echinostoma* larval stages. Acta Parasitol 59:502–509

4.2.10.1 Further Echinostomes

At least five further so-called snail-borne *Echinostoma* (syn. *Euparyphium*) species may infect humans. Only specialists are able to differentiate these species based on the arrangement of the hooks along the collar. Among these species *Echinostoma lindoense* is rather common. It was described as well in Indonesia (on the island Sulawesi) as in Brasilia. The life cycle of these five species runs very similar to that of *E. ilocanum*. Further related species are listed in Table 4.2.

4.2.11 *Gastrodiscoides hominis* and Related Species (Gastrodiscoidiasis)

1. **Name**: Greek: *gaster* = stomach; *discoides* = disc-like. Latin: *hominis* = belonging to humans. English: Amphistomal fluke.
2. **Geographic distribution/epidemiology**: In India, Indochina, Java, Philippines, Japan and Egypt at least five million persons are infected.
3. **Biology, morphology**: The adult hermaphroditic worms of *G. hominis* reach a size of 5–10 mm × 5 mm and are found in humans mainly attached in the colon and caecum. This worm is especially characterized by the features that the anterior pole has a rather small width, whereas the posterior pole looks plate-like and bears at its terminal end the ventral sucker. The eggs of this worm are excreted within human feces. The further development is very similar to that of *Fasciolopsis buski*. Rats and pigs are "reserve final hosts" and the snail families Planorbidae and Lymnaeidae offer several species which act as intermediate

Fig. 4.18 (continued) vermicularis; (**8**) *Trichuris trichiura*; (**9**) *Ascaris lumbricoides* (fertilized); (**10**) *Ancylostoma duodenale* and *Necator americanus*; (**11**) *Diphyllobothrium latum*; (**12**) *Hymenolepis microstoma*; (**13**) *Paragonimus westermani*; (**14**) *Trichostrongylus* sp.; (**15**) *Ascaris lumbricoides* (non-fertilized); (**16**) *Schistosoma japonicum*; (**17**) *Schistosoma haematobium*; (**18**) *Schistosoma mansoni*; (**19**) *Echinostoma* sp.; (**20**) *Fasciolopsis buski* and *Fasciola hepatica*; *B* blastomeres; *D* yolk cells, *E* egg cell, *M* miracidium larva, *O* oncosphaera larva, *OP* operculum, cover, *P* polar plug

Table 4.2 Further echinostomes

Species	Main final hosts	Intermediate hosts with infectious stages
Himasthla muehlensi	Seagulls	Mussels (*Mytilus, Mya*)
Hypoderaeum conoideum	Ducks, geese	Water snails
Aretyfechinostomum conoideum	Pigs, rats	Water snails (*Indoplanobarius*)

hosts. The **infection of humans** occurs by oral uptake of metacercariae that are attached to water plants.

4. **Symptoms of the disease**: Only in cases of massive infections, symptoms like diarrhoea and abdominal pain were noted

5.–11. **Diagnosis up to therapy**: Most details are similar to those in *Fasciolopsis buski* (Sect. 4.2.5).

4.2.12 *Watsonius watsoni* (Watsoniasis)

1. **Name**: The species was named according to its English discoverer William Watson (1715–1787).
2. **Geographic distribution/epidemiology**: Focally in Europe, Africa and Asia, but apparently only a few humans are infected.
3. **Biology, morphology**: These flukes appear pear shaped and reach a length of up to 8–10 mm and a width of 4–5 mm, but are 4 mm thick. Their ventral sucker is situated at the posterior pole of the fluke. The adults parasitize along the surface of the whole intestine and their eggs are thus excreted within the human feces. They look very similar to those of *Fasciola hepatica*. Their development outside the body of final hosts is not yet well studied. However, there are indications that there are similarities to *Fasciolopsis buski*.
4. **Symptoms of the disease**: Strong diarrhoeas after a not yet defined incubation period.

5.–11. **Diagnosis until therapy**: See *Fasciolopsis buski* (Sect. 4.2.5).

Further Reading

Baron TH et al (2014) *Gastrodiscoides hominis* infestation of colon: endoscopic appearance. Gastrointest Endosc 79:549–550

Goswami LM et al (2009) Molecular characterization of *Gastrodiscoides hominis*. Parasitol Res 104:1485–1490

4.2.13 *Nanophyetus* Species (Nanophyetiasis)

1. **Name**: Greek: *nano* = small; *phyes* = living stage. Latin: *salmo* = salmon. English: American dog fluke.
2. **Geographic distribution/epidemiology**:

   In Northern waterrich regions of America and Russia, some human cases have been reported.
3. **Biology, morphology**: *N. salmincola* parasitizes predominantly inside the intestine of dogs, foxes and several fish-feeding raptors. The adult hermaphroditic worms reach a length of about 2.5 mm and a width of 0.5 mm. They are anchored by the help of their two suckers inside the crypts of the small intestine. The 82–97 µm × 38–55 µm sized eggs are excreted containing a larva in a multicellular stage. Outside of the body it takes 87–200 days until the miracidium larva is formed inside the egg, which starts the formation of the miracidium larva only when the egg is covered by water. Hatched miracidium larvae penetrate into water snails. Having entered these snails, the miracidium larva is transformed into a redia (skipping the sporocyst stage). Inside each redia 74–76 cercariae are formed, which are characterized by a very short tail. These cercariae are set free within the slime of the snail and are able to penetrate into the skin of at least 34 species of fish. Inside the skin of these fish, they are transformed into so-called metacercariae, which develop themselves into adult worms, after they have been ingested by the fish eating final host. Inside the intestine of these final hosts, these metacercariae reach maturity with 6–7 days and start egg production.
4. **Symptoms of the disease**: In humans and other final hosts the growing and adult worms do not lead to significant severe symptoms of disease. However, rickettsial agents of diseases such as **salmon poisoning disease** may even kill infected dogs. This severe disease or similar ones, however, have not yet been detected until now in humans.
5. **Diagnosis**: Microscopically detection of the large non-embryonated eggs in the feces of the final hosts.
6. **Pathway of infection**: Orally by ingestion of metacercariae within raw meat of fish. Infections are common in fish such as salmons or trouts.
7. **Prophylaxis**: Fish meat should only be eaten when cooked, roasted or stored in salt solutions.
8. **Incubation period**: In the case of humans, the timing of the occurrence of clinical symptoms after ingestion of metacercariae is unknown, but in dogs it takes only 1–2 weeks until symptoms of disease occur.
9. **Prepatent period**: 1–15 weeks.
10. **Patency**: Up to 1 year.
11. **Therapy**: See *Fasciolopsis buski*.

Further Reading

Ferguson JA et al (2010) Persistance of infection by metacercariae of *Apophallus* sp., *Neascus* sp. and *Nanophyetus salmincola*. J Parasitol 96:340–347

Fritsche TR et al (1989) Praziquantel for treatment of human *Nanophyetus salmincola* (*Troglotrema salmincola*) infection. J Infect Dis 160:896–905

Sandell TA et al (2015) Infections by *Renibacterium salmoniarum* and *Nanophyetus salmincola*. J Fish Dis 38:365–378

4.2.14 *Metorchis conjunctus* (Meteorchiasis)

1. **Name**: Greek: *meta* = behind; *orchis* = testes. Latin: *conjunctus* = connected.
2. **Geographic distribution/epidemiology**: North America, Canada; rather few humans are infected.
3. **Biology, morphology**: These flukes measure 1–7 μm × 0.5–2 mm and parasitize as adult mainly in dogs but only rarely in humans. The infection of humans and dogs occurs due to the oral intake of metacercariae, which occur encysted inside of the second intermediate hosts (freshwater fish).
4. **Symptoms of the disease**: The symptoms are similar to those, which occur in infections with *Clonorchis sinensis* (Sect. 4.2.3.1).
5. **Diagnosis**: Demonstration of eggs inside feces and bile fluid.

6.–11. **Pathway of infection until therapy**: Similar to *Clonorchis sinensis* (Sect. 4.2.3).

Further Reading

Mordvinov VA et al (2012) *Opisthorchis felineus* and *Metorchis bilis* are the main agents of liver fluke infection of humans in Russia. Parasitol Int 61:25–31

Sherrard-Smith E et al (2009) Distribution of Eurasian otter biliary parasites *Pseudoamphistomum truncatum* and *Metorchis albidus*. Parasitology 136:1015–1022

4.2.15 *Philophthalmus* Species

1. **Name**: Greek: *philein* = to love. Latin: *ophthalmicus* = belonging to the eye. English: eye fluke.
2. **Geographic distribution/epidemiology**: Worldwide, however, there are only very few publications considering human infections.
3. **Biology, morphology**: The hermaphroditic adult worms live on or in the eyes of birds, while their larvae are found inside snails.
4. **Symptoms of the disease**: If adults are attached at the cornea of their hosts, a typical, often severe conjunctivitis may occur. However, if the worms stay in a subconjunctival position mostly only local irritations are introduced.

5. **Diagnosis**: Inspection of the eyes in the case of occurring irritations.
6. **Pathway of infection**: The infection of humans as well as that of birds apparently occurs when these hosts swim in lakes. Then water-borne cercariae may enter into the nasopharyngeal cavity and may migrate via the lacrimal channel into the eye and penetrate the conjunctiva.
7. **Prophylaxis**: Avoid bathing in lakes with huge numbers of water birds.
8. **Incubation period**: Some days after penetration of the carcariae.
9. **Prepatent period**: 1–2 weeks.
10. **Patency**: Up to 1 year.
11. **Therapy**: Chirurgical removal of penetrated worm stages.

Further Reading

Heneberg P et al (2014) Focal *Philophthalmus gralli* infection possible persists in *Melanoides tuberculate* over two years following the definitive host's removal. Parasitol Int 63:802–807

Literak I et al (2013) Eye trematode infection in small passerines caused by *Philophthalmus lucipetus* an agent with a zoonotic potential. Parasitol Int 200:390–396

Pinto HU, De Melo AL (2013) Taxonomic comments on South American species of *Philophthalmus*. Parasitol Int 62:483–484

4.3 Tapeworms (Cestodes)

The system of the tapeworms, which are characterized by a (large) number of flattened proglottids (repeated units) and a scolex, which bears systems with species-specific hold-fast organs (e.g. suckers, hooks, etc.). The medicinal and economically important tapeworms are grouped into two systems:

– The economically and medicinally less important group of **Cestodaria** shows 10 hooks at their larvae, which thus are described as **decacanth**.
– The economically and medicinally important group of **Eucestoda** is characterized by the occurrence of only **six hooks** at the surface of their larvae (**hexacanth**).

The two systems listed here are still today not really convincing. Therefore, the below listed groups are far from being settled in their position. However, this list gives a survey of important groups with respect to different interpretations:

Traditional System (Extract)
Phylum: PLATYHELMINTHES
Class: Cestoda (extract)
1. Subclass Cestodaria: (decacanth larvae, 10 hooks)

(continued)

Order: Amphilinidea
Order: Gyrocotylidea

2. Subclass Eucestoda: (hexacanth larvae, six hooks)

e.g. Order Caryophyllidea
Order: **Pseudophyllidea**
Family: Diphyllobothridae
Order: Proteocephalea
Order: **Cyclophyllidea**
Family: Dioecocestidae
Family: Hymenolepididae
Family: Taeniidae
Family: Mesocestoididae
Family: Dilepididae
Family: Davaineidae
Family: Anoplocephalidae
Family: Dipylididae

Phylogenetic System (extract)

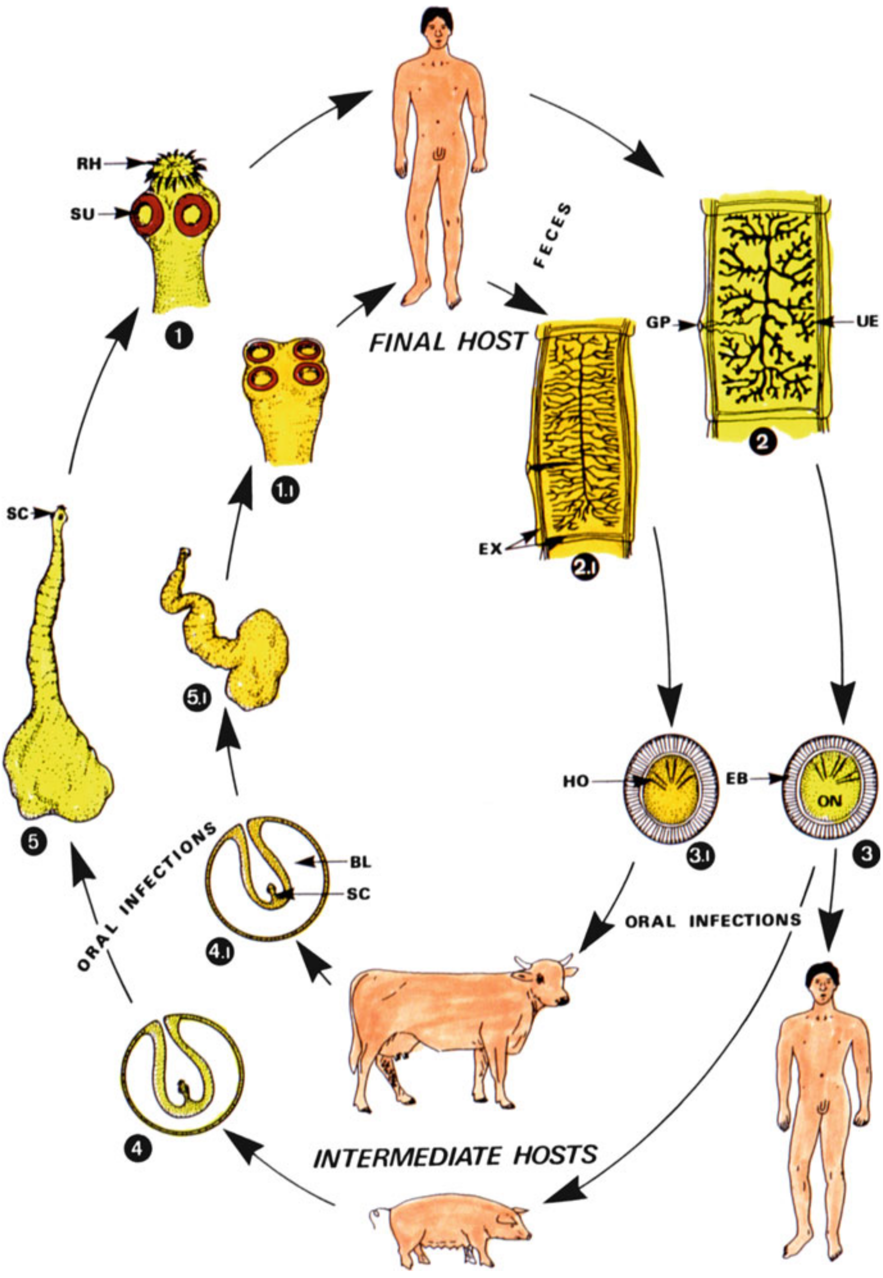
Phylum: PLATYHELMINTHES

- Cercomeromorphae
  - Monogenea
  - Cestoda (=tapeworms at large)
    - Gyrocotylidae
    - Nephroposticophora
      - Amphilinidea
      - Cestoidea (=tapeworms in a narrow sense)
        - Caryophyllidea
          - Eucestoda
          - (Families like in the above cited traditional system)

The most important parasites of humans are classified in the orders **Pseudophyllidea** and **Cyclophyllidea**.

4.3.1 *Taenia solium, T. asiatica* (Pork Tapeworm) (Taeniasis)

1. **Name**: Greek: *tainia* = tape. Latin: *solus* = only. English: Pork tapeworm.
2. **Geographic distribution/epidemiology**: Worldwide. Besides *Taenia solium* a second species exists in Asia: *Taeni*a asiatica, which does not show much difference to *Taenia solium* morphologically, but with respect to molecular biology it is more similar to *T. saginata*.
3. **Biology, morphology**: The adults of *Taenia solium* reach a length of 4–6 m in humans (final host) and may stay alive for more than 20 years. Their head (scolex) measures 1–2 mm in diameter and is provided with four suckers and a crown of hooks. This crown of hooks comprises 26–32 large (160–180 μm) and small (120–150 μm) hooks (Figs. 4.19 and 4.20). The Asian species (*T. asiatica*)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ORAL INFECTIONS
4
INTERMEDIATE HOSTS

Fig. 4.19 Life cycles of *Taenia solium* (1–5) and *T. saginata* (1.1–5.1). (**1**–**2.1**) Adult worms live exclusively in the intestine of man and reach a length of 4–6 m (*T. solium*) or 6–10 m (*T. saginata*) often with about 2000 proglottids. The scolex of *T. solium* is endowed with an armed rostellum (**1**). The terminal proglottids (10–20 × 5–7 mm) are characterized by a typically branched uterus filled with up to 100,000 eggs. On each day 6–7 of these proglottids detach and may either pass out with the feces or actively migrate out of the anus (**3**, **3.1**). As an excreted proglottid begins to dry up, a rupture occurs along the midventral and terminal regions and allows eggs to escape. The spherical

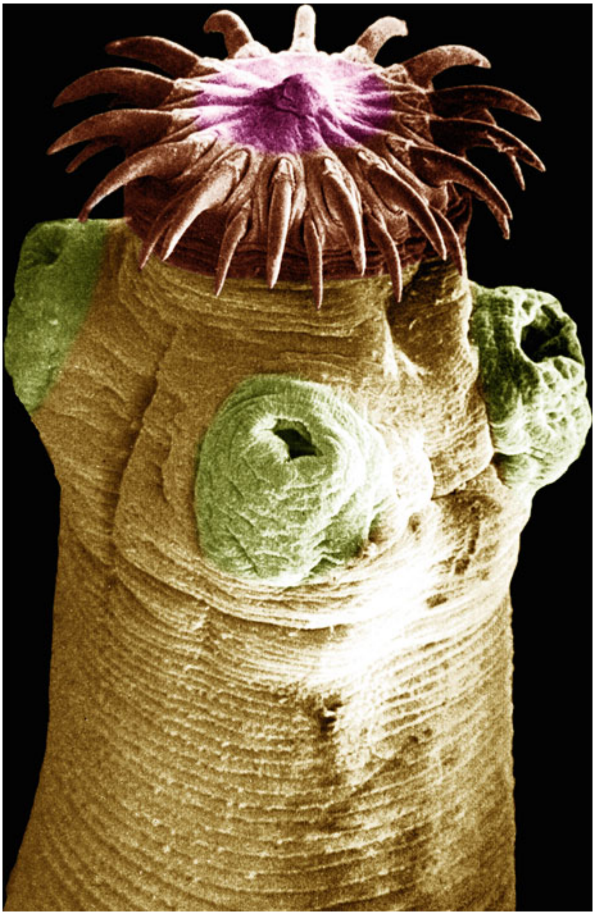

Fig. 4.20 Scanning electron micrograph of the scolex of *Taenia* sp. (type of *T. solium*) with four suckers and typical crown of hooks at the rostellum

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Fig. 4.19 (continued) eggs (40–45 µm; indistinguishable between species) originally have a hyaline outer membrane (eggshell) which is usually lost by the time the eggs are voided with the feces. Thus, the eggs are bordered by a thick, striated embryophore surrounding the oncosphaera (ON). (**4**, **4.1**) When ingested by the intermediate host, the oncosphaera hatches in the duodenum, penetrates the mucosa, enters a venule and is carried throughout the body. A bladder worm (cysticercus) of about 7–9 × 5 mm is formed, reaching infectivity in about 2 months (*C. cellulosae* in *T. solium*; *C. bovis, C. inermis* in *T. saginata*). When humans ingest eggs of *T. solium* or a terminal proglottid is destroyed inside the intestine, cysticerci may also readily develop in many organs including brain and eyes. These infections lead to severe dysfunctions depending on the parasitized organ (cysticercosis). (**5**) A person becomes infected when a bladder worm is eaten along with raw or insufficient cooked meat. The evaginating scolex becomes attached to the mucosa of the small intestine and matures in about 5–10 weeks. *BL* bladder of cysticercus, *EB* embryophore, *EX* excretory vessels, *GP* genital pore, *HO* hooks of oncosphaera, *ON* oncosphaera, *RH* rostellar hooks, *SC* scolex, *SU* sucker, *UE* uterus filled with eggs

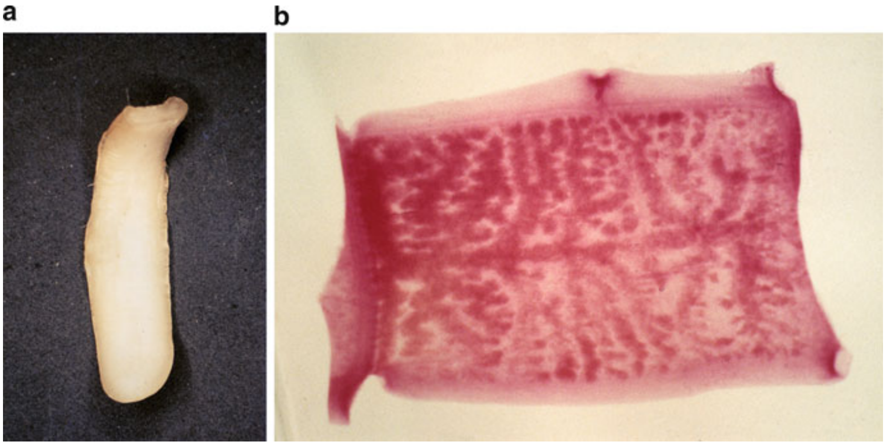

Fig. 4.21 Light micrographs. (**a**) Unstained freshly excreted proglottid. (**b**) *Carmine red*-stained proglottid showing the branches of the uterus

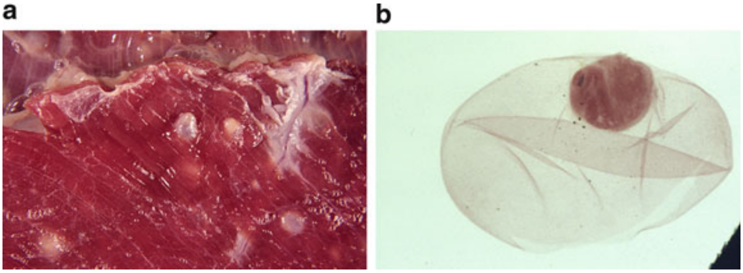

Fig. 4.22 Macrophotos of stages of *Taenia solium*. (**a**) Cysticerci within meat of pigs. (**b**) Cleaned cysticercus showing inside the bladder the anlage of the head region

shows as an adult only a few remnants of crown hooks. The uterus of the terminal proglottids contains up to 80,000 eggs of 30–45 μm size. These eggs cannot be distinguished from those of *T. saginata* (Fig. 4.21a, b). Each terminal proglottid becomes ruptured from anterior portion of the tapeworm at its front part. This is why eggs may be discharged from the uterus during the contraction of the proglottid still in the intestine. In this case, eggs should be found in stool as well. Additionally the proglottids can produce creeping movements in fresh stool, attached at skin around the anus and/or in the underwear of an infected person. The proglottids have been often kept for independent individuals. The eggs contain already the infectious 6-hook larvae (oncosphaera) when they are discharged in human stool (Figs. 4.18 and 4.27). After ingestion of the eggs by a pig, the oncosphaera hatches from the egg inside the intestine, infiltrates different organs and transforms itself to the so-called cysticercus cellulosae larva (Fig. 4.22a, b). This stage, also called metacestode, is rather big since it measures 0.6–2 cm × 0.5–1 cm in diameter. It already contains the invaginated

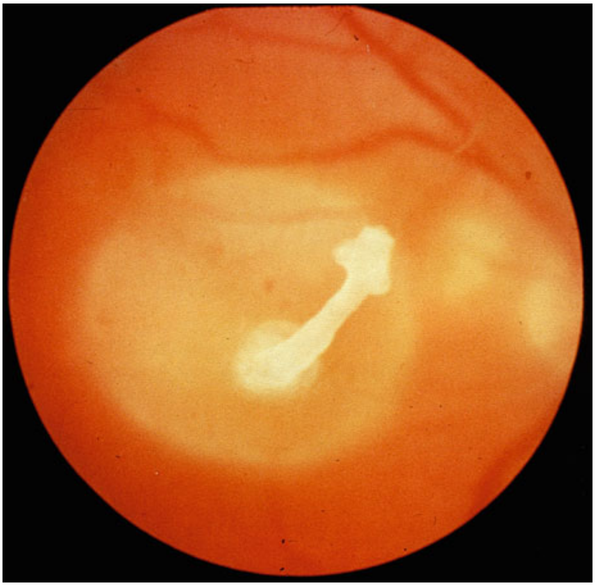

Fig. 4.23 *Taenia solium*. Protruded cysticercus in the eye of a human

head of the adult tapeworm and becomes infectious for humans within 2–4 months. The life cycle goes on with the infection of humans, if they consume metacestodes inside insufficiently cooked meat of pork. After 8–12 weeks, the tapeworm reaches maturity in the human intestine and then starts to release proglottids, which are discharged within the feces.

On the other hand, it may happen that humans ingest tapeworm eggs containing an oncosphaera larva when eating egg-contaminated vegetables or food onto which eggs had been transported by flies. In these cases, humans can get cysticercosis in different organs such as muscle, eye, brain, a.s.o. (Figs. 4.23 and 4.24). This type of infection may also occur, if humans bearing an adult tapeworm get in contact with their own feces and thus may ingest tapeworm eggs.

4. **Symptoms of the disease (Taeniasis, cysticercosis)**: In the case of a persisting infection with an adult *Taenia solium* tapeworm symptoms are scarce. The main indications are loss of body weight, abdominal pain, disturbed digestion, itching around the anus (because of creeping proglottids), and a strong feeling of hunger, which alternate with anorexia. Further unspecific effects due to the excreted metabolites of the worm still have to be investigated. A slight eosinophilia may be diagnosed in the peripheral blood. In the case that the brain is infected (with cysticercosis, neurocysticercosis) related disturbances will occur.
5. **Diagnosis**: The proglottids are whitish, rectangular and motile (Fig. 4.21a). Thus, the infected patient mostly detects them himself. About 6–10 proglottids are discharged daily. A differentiation between *T. solium* and *T. saginata*

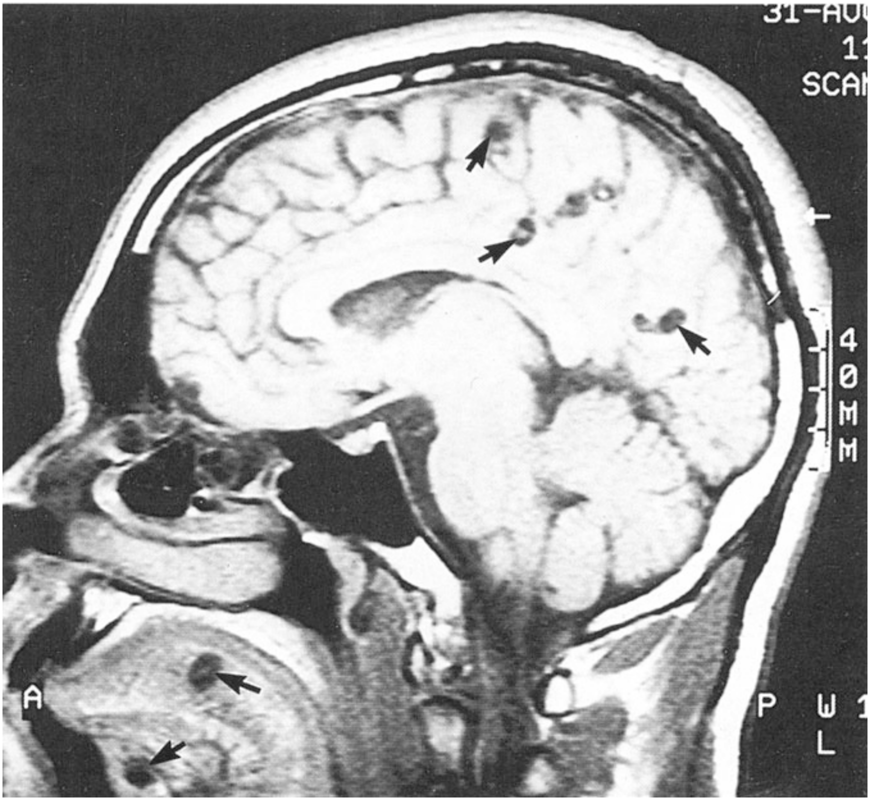

Fig. 4.24 Scanning photo of a human head, where cysticerci have been formed inside the brain (*arrows*)

should be made, but only after fixation of the excreted proglottids due to the danger of an infection with *T. solium*. The diagnosis can be done easily by observing the number of the branches of the uterus inside the proglottids. The uterus of *T. solium* mostly shows 7–10 branches at each side, while *T. saginata* proglottids have at least 12 (mostly 20–35) branches at each side. The counting of these branches should be done after staining the uterus of the proglottids by injection of ink into the lateral genital papilla and pressing the thus prepared proglottids between two slides. Microscopically investigation will show the results. Further signs of differentiation between the two species can be observed after fixation of the whole mature proglottid: *T. solium* possesses threefold lobed ovarium; *T. saginata* has a vaginal sphincter. The number of excreted eggs in the stool is rather low and intermitting, because the uterus is fully closed so that eggs are set free only by bursting or by digestion of the proglottids in the intestinal lumen of the host. In the case that there are no proglottids excreted several enrichment methods (sedimentation, flotation) should be used repeatedly to obtain the eggs. Unfortunately the thick-walled eggs (30–40 μm) of the different *Taenia* species appear identical and do not allow an identification of the species. A reliable differentiation, however, can be reached with an acid-resistant staining (Ziehl–Neelsen), whereby only the eggs of *T. saginata* appear coloured. A clear identification can be made based on the scolex, if it is spontaneously excreted of after a therapy. However, the use of modern anthelmintics mostly causes the lysis of the anterior portion of the tapeworm including the scolex. The determination of coproantigens (by the help of ELISA) is possible in most cases and is used in control campaigns. The proof of antibodies in the blood is only important in the case of a suspected cysticercosis. An eosinophilia of the blood is rather uncommon in the cases of exclusive intestinal infection. The cysticerci (up to 18 mm) in the brain can be proven by imaging methods (CT, MRT).

6. **Pathway of infection**: The oral consumption of cysticerci in raw or insufficient cooked meat leads to an infection with adult tapeworms in the intestine of humans. The oral consumption of worm eggs containing the oncosphaera larva leads to the occurrence of cysticerci in different organs of humans only in the case of *T. solium*. Cysticerci do not appear in cases of *T. asiatica* and *T. saginata*.
7. **Prophylaxis**: Avoidance to eat raw or semi-cooked pork. In the case of *T. asiatica* raw meat of goats, bears, monkeys, dogs and cattle should not be eaten in a raw or “English” style (=bloody status). Freezing (−18 °C) for a long time (24 h at least) kills the cysticerci. Avoiding fecal contamination (i.e. at wild camping sites, parking at picnic areas) is highly recommended.
8. **Incubation period**: In the case of an infection with adult tapeworms: 8 weeks; in case of infestation with cysticerci 4–10 weeks (severity of the symptoms depends on the afflicted organs).
9. **Prepatent period**: 8–18 weeks (first occurrence of proglottids in the stool); *T. asiatica*: 4 weeks.
10. **Patency**: Adult worms in humans: up to 20 years. The cysticercus in the pig remains infectious for 1–2 years. Immunity does not occur.
11. **Therapy**: The treatment of choice is praziquantel (10 mg/kg bodyweight as a single dosage) with up to 100 % healing rate. As well effective are niclosamide (1 × 2 g) and mebendazole (2 × 200 mg daily for 3 days). The administration of laxantia (ricinus oil) accelerates discharging of the dead worm and prevents from new self-infections with eggs. Therapy controls should be done after 3 months. Precautions have to be considered in the case of the presence of infectious *T. solium* eggs: the use of gloves and disinfection fluids is highly recommended while working with adult proglottids and stools of infected persons. In the case of a neurocysticercosis, the patient has to be treated with antihistamines in slowly increased doses to prevent a shock reaction after application of praziquantel. Ocular infestation must be treated surgically.

Further Reading

Ash A et al (2015) Controlling *Taenia solium* and soil transmitted helminths in a northern Lao PDR village: impact of a triple dose albendazole regime. Acta Trop. doi:10.1016/j.actatropica.2015.05.018

Gabriel S et al (2015) Human migration and pig/pork import in the European Union: what are the implications for *Taenia solium* infections? Vet Parasitoll 213: 38–45

Mehlhorn H et al (1981) On the nature of the proglottids of cestodes: light and electron microscope studies of *Taenia*, *Hymenolepis* and *Echinococcus*. Parasitol Res 65:243–259

4.3.2 *Taenia saginata* (Cattle Tapeworm) (Taeniasis)

1. **Name**: Greek: *tainia* = tape. Latin: *sanguinatus* = strong, fat.
2. **Geographic distribution/epidemiology**: Worldwide, hundreds or thousands, especially in countries of cattle production.
3. **Biology, morphology**: The adults of *Taenia saginata* in humans (final host) have a length of 6–10 m and thus are larger than *T. solium* (Fig. 4.19). The head (scolex) measures 1–2 mm in diameter and has 4 suckers but no hooks (opposite to *T. solium*). Their final proglottids are larger than those of *T. solium*, being 20 mm long and 7 mm wide. That is why the uterus with its more than 20 lateral branches has more space for egg storage (up to 100,000 eggs). The life cycle of *T. saginata* is similar to that of *T. solium*, but the intermediate hosts are cattle. The life cycle ends with the infection of humans by ingestion of cysticerci (*Cysticercus inermis* or *C. bovis* metacestodes; measuring 7–9 × 5 mm in size) within raw or insufficient cooked beef.
4. **Symptoms of the disease (Taeniasis)**: See *T. solium* (Sect. 4.3.1).
5. **Diagnosis**: In the case of *T. solium* (Figs. 4.18 and 4.27), eggs of *T. saginata* can be diagnosed by an anal-touch test, which is also used in cases of enterobiasis. The eggs glue at the perianal skin with their sticky surface, if proglottids were disrupted in the intestine. Discharged proglottids may remain motile on the skin or in the underwear of the patients.
6. **Pathway of infection**: Ingestion of raw or insufficiently cooked beef which contains cysticerci. Immunity does not occur.
7. **Prophylaxis**: Avoiding the ingestion of raw or nearly raw beef (18 °C deep freezing of beef for 24 h kills the parasites).
8. **Incubation period**: 8–12 weeks (symptoms are mostly missing).
9. **Prepatent period**: 8–12 weeks.
10. **Patency**: 25 years (maybe for lifetime).
11. **Therapy**: See *T. solium* (praziquantel 1 × 10 mg/kg bodyweight).

Further Reading

Dupuy C et al (2014) Prevalence of *Taenia saginata* cysticercosis in French cattle in 2010. Vet Parasitol 203:65–72

Rostami S et al (2015) Genetic variability of *Taenia saginata* inferred from mitochondrial DNA sequences. Parasitol Res 114:1365–1376

Tembo A, Craig PS (2015) *Taenia saginata* taeniosis: copro-antigen time-course in a voluntary self-infection. J Helminthol 89:612–619

Zanetti Lopes WD et al (2014) History of therapeutic efficacy of albendazol sulphoxide administered in different routes, dosages and treatment schemes, against *Taenia saginata* cysticercus in cattle experimentally infected. Exp Parasitol 137:14–20

4.3.3 *Diphyllobothrium latum* Species (Broad Tapeworm) (Diphyllobothriasis)

1. **Name**: Greek: *di* = two, double; *phyllon* = leaf; *bothros* = depression, slit. Latin: *latus* = big, large. The adult worms are provided with two elongated bothria at the scolex as hold-fast system, which guarantees firm attachment at the intestinal wall.
2. **Geographic distribution/epidemiology**: At least two species occur close to the sea coast or in lakes: *Diphyllobothrium latum*: Baltic Sea region, Volga basin; Lake Constance area, Swiss, Italy, Danube delta, Middle East, Siberia, Mandschuria, Japan, North America, Eastern Asia, Australia, Africa. *D. pacificum* is common in South America, especially in Chile and Peru. Other species are *D. klebanovski* and *D. nihonkaiense* in Eastern Asia and *D. dendriticum* in freshwater.
3. **Biology, morphology**: Both species (*D. latum*, *D. pacificum*) look very similar. They live as adults longer than 10 years in the intestine of humans or in other final hosts such as cats and dogs (seals in case of *D. pacificum*). The scolex is attached by the help of its two suckers (=slit-like bothria) at the intestinal wall) (Figs. 4.25 and 4.26). The broad tapeworm can reach a length of up to 20 m, especially if solitary. Then it can develop up to 4000 proglottids. If 10–14 individuals are found in the intestine of a human host, they are less than 2 m long only. The mature proglottids are 2 cm wide and are significantly wider than long. Since the uterus has an own opening, the 60–70 μm × 45–55 μm sized eggs (Fig. 4.18) are able to leave the proglottids already inside the intestine, so that they can be found in the feces. Thus, the last 3–5 proglottids are then early empty and were discharged together as a short tape. The operculated eggs, which are set free within the feces, do not yet contain a larva, which, however, is developed as soon as these eggs (Fig. 4.27e) become surrounded by sweet or brackish water. About 9–12 days after such eggs had entered water, the **coracidium** larva is ready to hatch from the egg by blasting the cover (=operculum). The coracidium larvae are covered by a layer of cilia, which enables them to swim around. Inside (below the ciliated epithelium) the

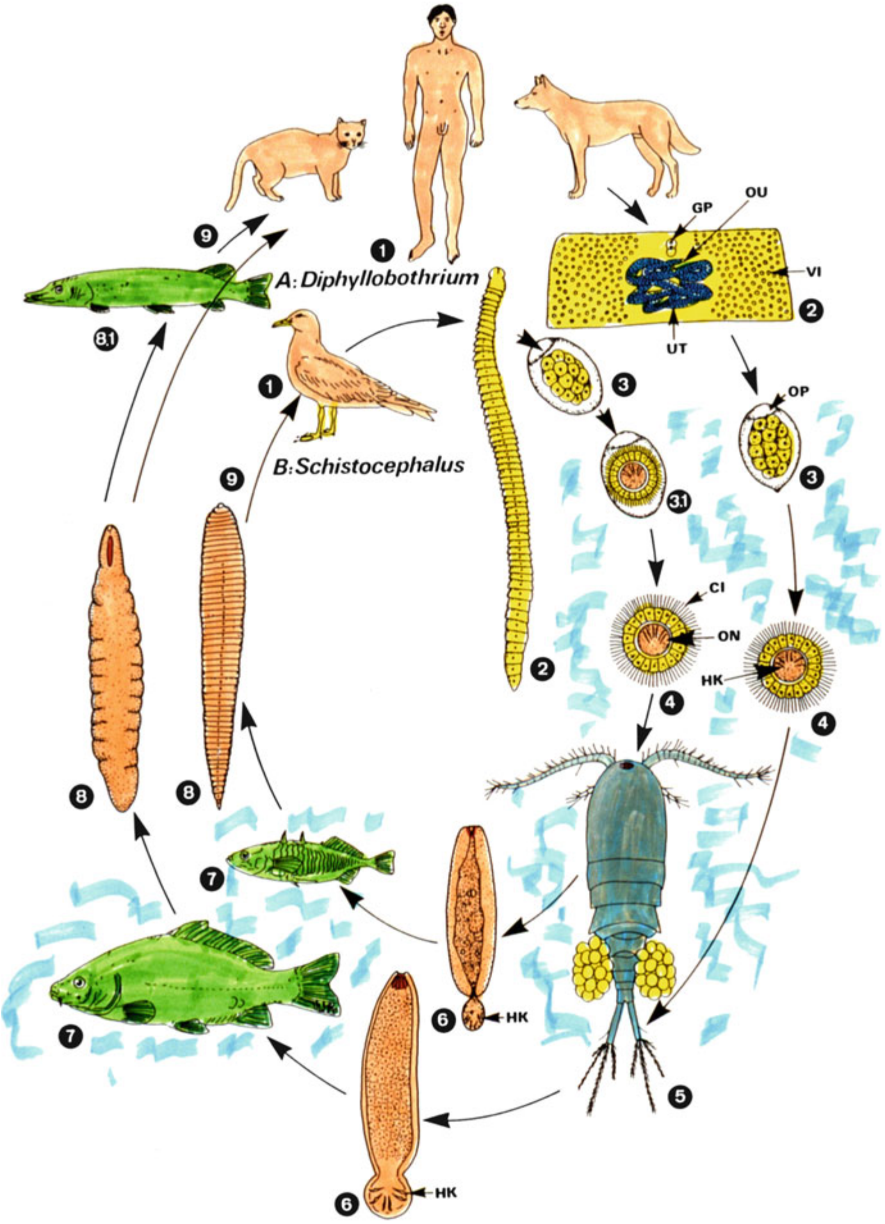

Fig. 4.25 Life cycle of pseudophyllidean cestodes. (**A**) *Diphyllobothrium latum* inhabits the intestine of human, cats, dogs and other fish-eating animals (final hosts), being attached to the intestinal wall with two longitudinal bothria. (**B**) *Schistocephalus solidus* occurs in the intestine of a wide range of fish-eating birds. *Ligula intestinalis* has a very similar life cycle. (**1**) Final hosts. (**2**) Adults. *D. latum* reaches a maximum length of 25 m; its mature proglottids are broader than long; coils of the gravid uterus form a centrally located rosette. *S. solidus* is lanceolate shaped with a size of 5–8 × 1 cm, bothria-like apical indentations are of poor adhesive power. (**3**) The operculated eggs are excreted unembryonated; completion of development to coracidium larva (**3.1**) takes one to several weeks depending on the water temperature. (**4**) Free coracidium larva containing the

infectious 6-hook larva (oncosphaera) has been formed in the meantime. As soon as the first intermediate host (a copepod) has ingested the coracidium larva develops into the so-called **procercoid** larva. If a fish (the second intermediate host) has ingested the **procercoid** larva, it develops into the **plerocercoid** larva (=**sparganum**). Such larvae are enriched inside predator fish (e.g. in pikes). If fish infested with such plerocercoid larvae are eaten by humans or some (other) mammals, the plerocercoid larvae grow up to the adult tapeworms (Figs. 4.25 and 4.26a). The related species *D. dendriticum* has a life cycle involving freshwater fish and seagulls.

4. **Symptoms of the disease (Diphyllobothriasis)**: An infection with *D. latum* may persist for a long time without any symptoms of disease. Only after weeks the worm starts to increase its length daily for 9–15 cm and severe symptoms of disease may be initiated. The most important effect is surely the introduction of a peculiar type of anaemia (**pernicious** type) as a consequence of the permanent withdrawal of vitamin B_{12}. This type was especially often noted in patients, when the tapeworm was attached close to the pylorus region in the intestine (=in the duodenum). Long-lasting infections with *D. latum* may also lead to neurologic disorders besides weakness, paraesthesias, motor dysfunctions, etc.
5. **Diagnosis**: The existence of a *D. latum* infection can rather easily be obtained by fecal examination showing the typical operculated eggs (Fig. 4.27e). These eggs of *D. latum* measure 60–70 µm × 45–55 µm, while the eggs of the South American species *D. pacificum* are considerable smaller (50 µm × 40 µm). Since the egg excretion may vary considerably from day to day the use of enrichment methods (M.I.F.C., S.A.F.) is recommended or a repeated investigation.

Fig. 4.25 (continued) oncosphaera which is endowed with six hooks. (**5–6**) Having ingested free coracidia several species of copepods are suitable intermediate hosts within which development of second-stage larvae (procercoid, **6**) occurs. (**7–8**) As second intermediate hosts, brackish and freshwater fish become infected by ingesting infected copepods. Inside the intestine the procercoid is released and eventually bores its way into the body cavity and muscles where it grows rapidly into a plerocercoid (sparganum). In *D. latum* the plerocercoids remain mainly undifferentiated, whereas in *S. solidus* the plerocercoids show the main features of the adults (i.e. division into 62–92 proglottids and the presence of genital anlagen; however, they are not yet fertile). Unlike *D. latum*, the progenetic plerocercoids of *S. solidus* are extremely specific in their host, developing only in the body cavity of the marine and freshwater forms of the 3-spined stickleback (*Gasterosteus aculeatus*). (**8.1**) In *D. latum* plerocercoids may become accumulated without further development in the muscles (not encysted) of carnivorous fish (acting as paratenic host). (**9**) Infections of final hosts occur by ingestion of raw meat of fish containing plerocercoids. Having reached the intestine the plerocercoids of *D. latum* grow rapidly and become adult worms in 5–6 weeks, whereas *S. solidus* plerocercoids mature rapidly (within 36–48 h) and release eggs. Humans, who accidently eat meat of fish containing plerocercoids of other non-human pseudophyllidean tapeworms, may also become infected; however, plerocercoids do not mature, but creep around inside the human body, leading to a disease called **sparganosis**. *CI* cilia, *GP* genital pore, *HK* hooks of ON, *ON* oncosphaera, *OP* operculum, *OU* opening of the uterus, *UT* uterus, *VI* vitellarium

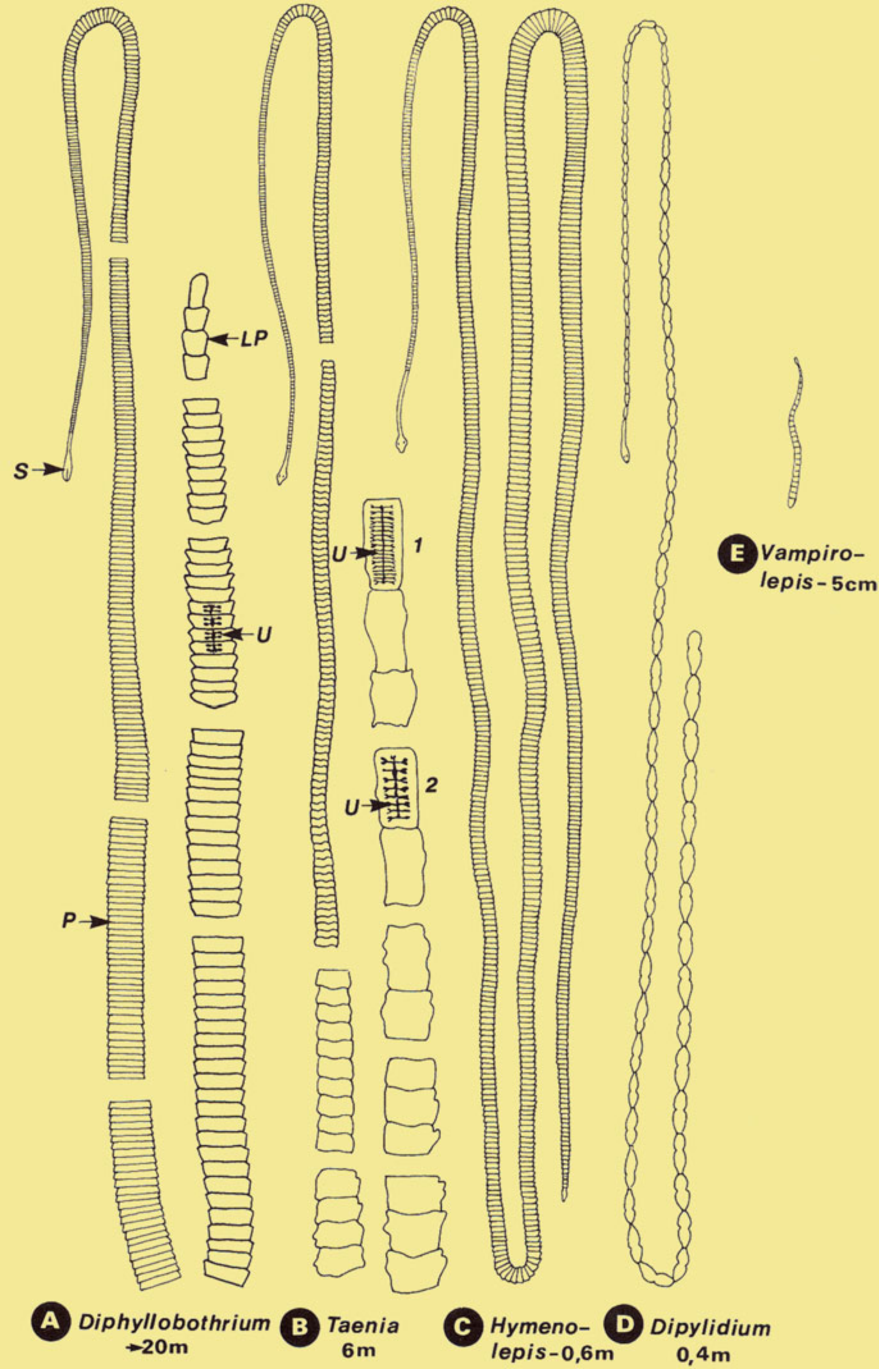
S
P
LP
U
U
1
U
2
E Vampiro-lepis-5cm
A Diphyllobothrium →20m
B Taenia 6m
C Hymeno-lepis-0,6m
D Dipylidium 0,4m

Fig. 4.26 Diagrammatic representation of the strobila of different tapeworms of humans. *LP* empty proglottids, *P* proglottids at different developmental stages, *S* scolex, *U* uterus

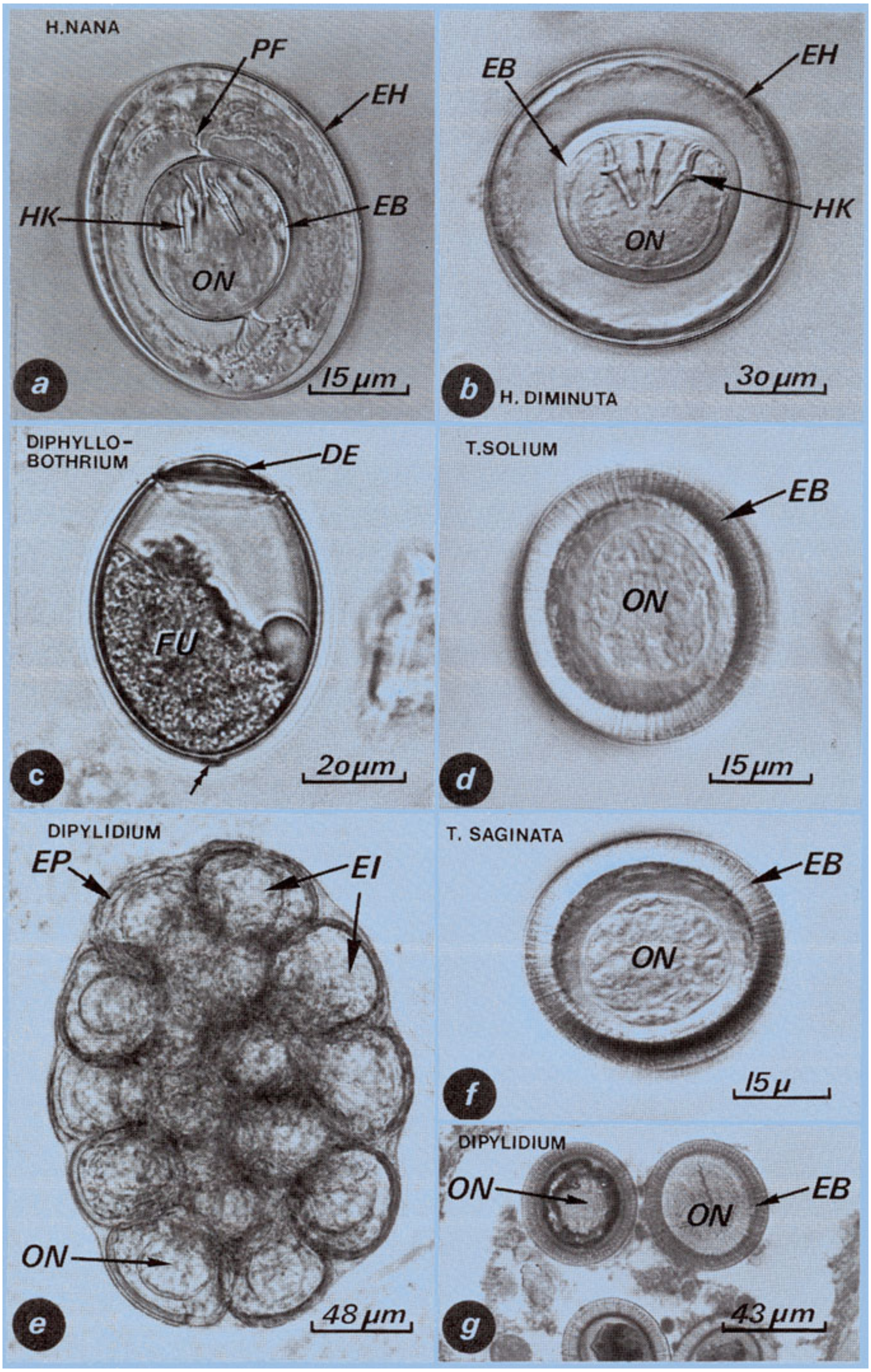
H.NANA
PF
EH
HK
EB
ON
15 µm
a
EB
EH
HK
ON
30 µm
b
H. DIMINUTA
DIPHYLLO-
BOTHRIUM
DE
FU
20 µm
c
T.SOLIUM
EB
ON
15 µm
d
DIPYLIDIUM
EP
EI
ON
48 µm
e
T. SAGINATA
EB
ON
15 µ
f
DIPYLIDIUM
ON
ON
EB
43 µm
g

Fig. 4.27 Light micrographs of eggs of important tapeworm species. *DE* cover, operculum, *EB* embryophore, *EH* egg shell, *EI* egg, *EP* package of eggs, *FU* developmental stage during cell division, *HK* hooks, *ON* oncosphaera larva, *PF* polar filament

6. **Pathway of infection**: The infection of humans occurs during oral uptake of plerocercoid larvae (spargana) with raw or undercooked fish muscles (fish from fresh or brackish water). Within 21–24 days after infection, the tapeworms reach the adult stage and produce already eggs, although they still grow every day for up to 15 cm. However, several young tapeworms do not reach maturity. Occasionally they penetrate the intestinal wall and migrate inside the body inducing the so-called **spargana disease**.
7. **Prophylaxis**: Fish from fresh or brackish water should never be eaten raw or undercooked. Deep freezing (18 °C) for at least 24 h kills potentially contained larvae.
8. **Incubation period**: In severe cases: 3 weeks; however, very often no symptoms occur for years.
9. **Prepatent period**: 21–24 days (=first occurrence of eggs in human feces).
10. **Patency**: Up to 10 years.
11. **Therapy**: Drug of choice is praziquantel (2.5–5 mg/kg bodyweight at a single application); niclosamide (2 g) as single dose is also effective. However, it is always recommended to substitute potential losses of vitamin B12. In order to avoid unsuccessful treatment stool controls have to be done three times per week for 3 weeks beginning about 6 weeks after the drug treatment.

Further Reading

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4.3.4 *Hymenolepis nana* and Other Species (Hymenolepiasis)

1. **Name**: Greek: *hymen* = thin skin; *lepis* = scale. Latin: *nanus* = dwarf. English: Dwarf tapeworm. In some literature, the genus name *Hymenolepis* has been changed to *Vampirolepis* or *Rodentolepis*.

2. **Geographic distribution/epidemiology**: Worldwide, especially in the tropics and subtropics; since about 80 million humans are infested (mainly children), *H. nana* can be considered as the most common tapeworm in humans.
3. **Biology, morphology**: *H. nana* parasitizes humans, mice and rats. The adult worms reach a length of about 5 cm and a width of 2–3 mm (Figs. 4.28 and 4.29). The scolex has a diameter of about 0.3 mm, has four suckers and is equipped with a protrudable, sphere-like rostrum with a single row of 20–24 hooks, which have a length of 140–180 µm (Fig. 4.29). Mature proglottids are

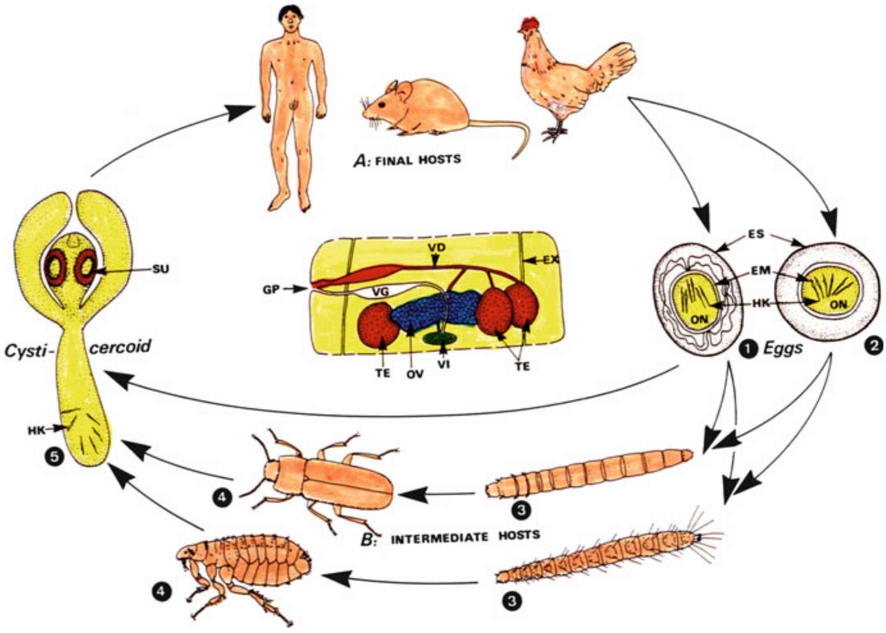

Fig. 4.28 Life cycle of tapeworms of the family Hymenolepididae. (**A**) Species and final hosts: *Rodentolepis* (*Vampirolepis, Hymenolepis*) *nana* (*fraterna*) of mice and humans, 4–6 cm long and 1 mm broad, scolex with 24–27 rostellar hooks; *Hymenolepis diminuta* of rats, mice, dogs and humans, up to 6 cm long and 3.5 mm broad, no rostellar hooks; *Echinolepis* (*Hymenolepis*) *carioca* of chicken and birds. Strobila up to 8 cm long and 3–5 mm broad; scolex has no rostellar hooks. The sexual mature proglottids are characterized by three spherical testes (TE); there is no distinct border wall between the proglottids (*dotted lines*). (**B**) Intermediate hosts: (**1**, **2**) Eggs containing the oncosphaera larva [(**1**) *H. nana*, 40–60 × 30–50 µm; (**2**) *H. diminuta* 60–80 × 70 µm] are infectious to various insects (larvae, adults) as intermediate hosts (**3**, **4**). (**5**) Inside the body cavity of these hosts a second larva (cysticercoid) is formed, which grows to become a mature tapeworm when the intermediate host is swallowed by the final host. In *H. nana* the intermediate host (**1**) is optional; when eaten by humans or rodents, the egg (**1**) hatches in the duodenum, releasing the oncosphaera, which penetrates the mucosa. Here it develops directly into a cysticercoid (**5**). In about 6 days the cysticercoid emerges into the lumen of the small intestine, where it attaches and grows to be a mature worm. *EM* embryophore (layer surrounding the oncosphaera), *EX* excretion system (longitudinal), *ES* eggshell, *GP* genital pores, *HK* hooks of oncosphaera; *ON* oncosphaera, *OV* = ovary (germarium), *SU* sucker, *TE* testes, *VD* vas deferens, *VG* vagina with enlarged seminal vesicle, *VI* vitellarium

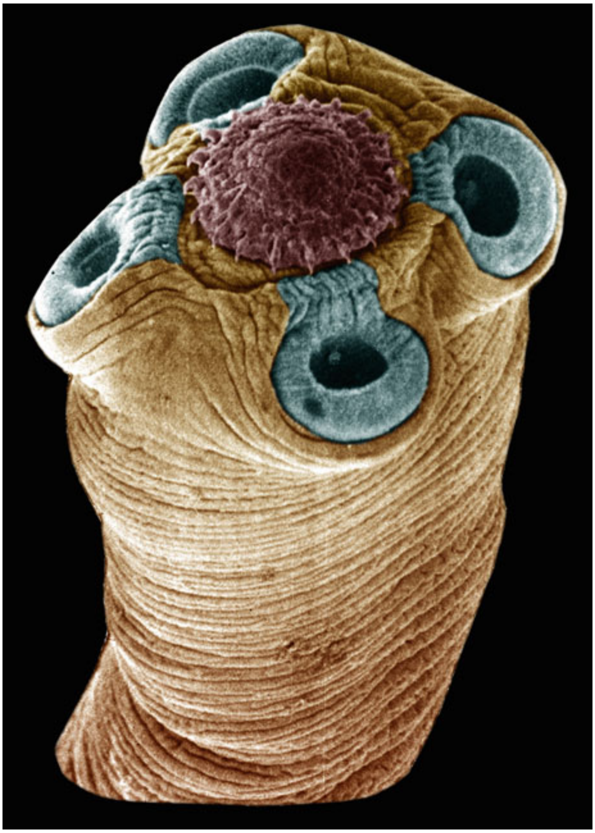

Fig. 4.29 Scanning electron micrograph: scolex of *Hymenolepis nana*

often destroyed already inside the host's intestine, so that the typical eggs (40–60 µm × 30–50 µm) are already found inside the feces (Figs. 4.18 and 4.27a). When insects (e.g. flour beetles or larvae of fleas) ingest such eggs, which already contain the oncosphaera larva, a so-called cysticercoid larva is also developed inside their body cavity. However, such a cysticercoid larva is developed in the intestine of humans if they ingest the eggs of *H. nana* from own or foreign feces. Thus, the intermediate host is only a facultative host in the life cycle of this peculiar tapeworm. Thus humans may become infected on three different ways:

(1) Oral uptake of cysticercoid larvae within undercooked or raw insects or parts of insects (insects are used as human food in Asia and other tropical countries).
(2) Oral uptake of *H. nana* eggs from human or rodent feces (this is apparently the predominant pathway in Europe).
(3) The oncosphaera larva, which is contained inside the egg is apparently able to hatch already inside the intestine of an infected person. Then it enters into the intestinal wall, develops there into the cysticercoid stage within

5–6 days and finally reaches again the lumen of the intestine, where it grows up to the adult worm. This process is described as endogenous autoinfection.

The whole development of the cysticercoid to reach the adult stage of the tapeworm takes in general about 3 weeks. However, adult *H. nana* worms live only for a few weeks, so that the often reported huge amounts of persisting worms are apparently due to repeated self-infections (autoinfections).

4. **Symptoms of the disease (Vampirolepiasis, hymenolepiasis)**: Immune competent humans develop a cell-derived immune reaction, which is able to suppress or to minimize repeated endogenous autoinfections and inflammations of the intestinal mucosa. In the case of infections of healthy adult persons mostly only very slight symptoms of disease occur (such as slight abdominal pain, slight cases of diarrhoea, which, however, may contain traces of blood, and weakness). Severe infections with huge numbers of worms, however, may occur in malnourished children, which then may accumulate these worms. This increases the severity of the symptoms and induces severe abdominal cramps, bloody diarrhoeas, loss of weight and a considerable blood eosinophilia.
5. **Diagnosis**: The feces contain typical eggs (Figs. 4.18 and 4.27a). Since egg production may vary, it is recommended to repeat feces control (flotation, M.I.F.C., S.A.F.). Blood eosinophilia may be a sign, too, which needs, however, confirmation by fecal tests.
6. **Pathway of infection**: Orally by uptake of cysticercoid larvae in portions of insects or by ingestion of eggs within fecally contaminated food.
7. **Prophylaxis**: Avoidance of oral contact to human or rat feces and avoidance to eat raw or undercooked insects.
8. **Incubation period**: 1–4 weeks; however, symptoms are often low grade and unspecific.
9. **Prepatent period**: 2–4 weeks.
10. **Patency**: 2 months; immunity is not reached—thus reinfections are possible.
11. **Therapy**: Drug of choice is praziquantel (25 mg/kg bodyweight) as a single dose, since it acts not only against adult worms but also against the cysticercoid larvae. Niclosamide (2 g daily) acts only against adults and thus has to be given for 7 days with a repetition after 3 weeks. Fecal controls are only reasonable 4 weeks after the end of treatment.

Further Reading

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Lin RJ et al (2014) Anthelmintic constituents from ginger (*Zingiber officinale*) against *Hymenolepis nana*. Acta Trop 140:50–60

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4.3.5 *Echinococcus* Species (Echinococciasis)

1. **Name**: Greek: *echinos* = hedgehook, spiky; *kokkos* = spherical. Latin: *granulosus* = granular; *multilocularis* = with several vacuoles inside. English: Tiny dog dwarf worm.
2. **Geographic distribution/epidemiology**: *E. granulosus*—worldwide; *E. multilocularis*—Southern Germany, focal in Germany, Austria, Switzerland, East until South of France, East Russia, North America, Hokkaido (island in North Japan); *E. vogeli*—in Uruguay. While *E. multilocularis* is found only in rare cases, *E. granulosus* infects several 100 thousand humans worldwide especially in countries with sheep breeding and numerous guard dogs. The adult worms live in predators (e.g. dogs, foxes, cats), while humans carry the extremely large larval stages.
3. **Biology, morphology**: The adult worms live in the intestine of carnivores (=final hosts). ***E. granulosus*** is predominantly found in dogs; however, it occurs also in foxes (Figs. 4.30, 4.31 and 4.32). The adult worms are hermaphrodites and reach a length of only 2.5–6.0 mm. The last terminal proglottid, which contains in a sack-like uterus the fertilized eggs, is the largest proglottid and mostly as long as the 1–3 anterior ones together. ***E. multilocularis*** occurs mainly in foxes—in some regions up to 30 % are infected. However, also dogs and cats might become infected, in case that they ingest infected intermediate hosts (=predominantly mice). *E. multilocularis* measures only 1–3 mm in length and this is considerably smaller than *E. granulosus* (Fig. 4.28 and Table 4.3). In both species, which occur often in large numbers (several thousand per animal) without inducing severe symptoms of disease, the terminal proglottid is regularly disrupted and excreted repeatedly at intervals of 7–14 days within the feces. In feces but also inside the fur of the final host the surface of these proglottids, ruptures and thus releases the spherical, 50 μm sized eggs, which already contain the infectious **oncosphaera** larva (=6-hook larva). Predominant intermediate hosts for *E. granulosus* are sheep; however, also ruminants, horses, pigs, rabbits, etc., may become infected as well as humans, where such an infection may be life-threatening.

   In the case of *E. multilocularis* rodents (mostly mice) serve as main intermediate hosts, but also humans may be infected and their organs will become

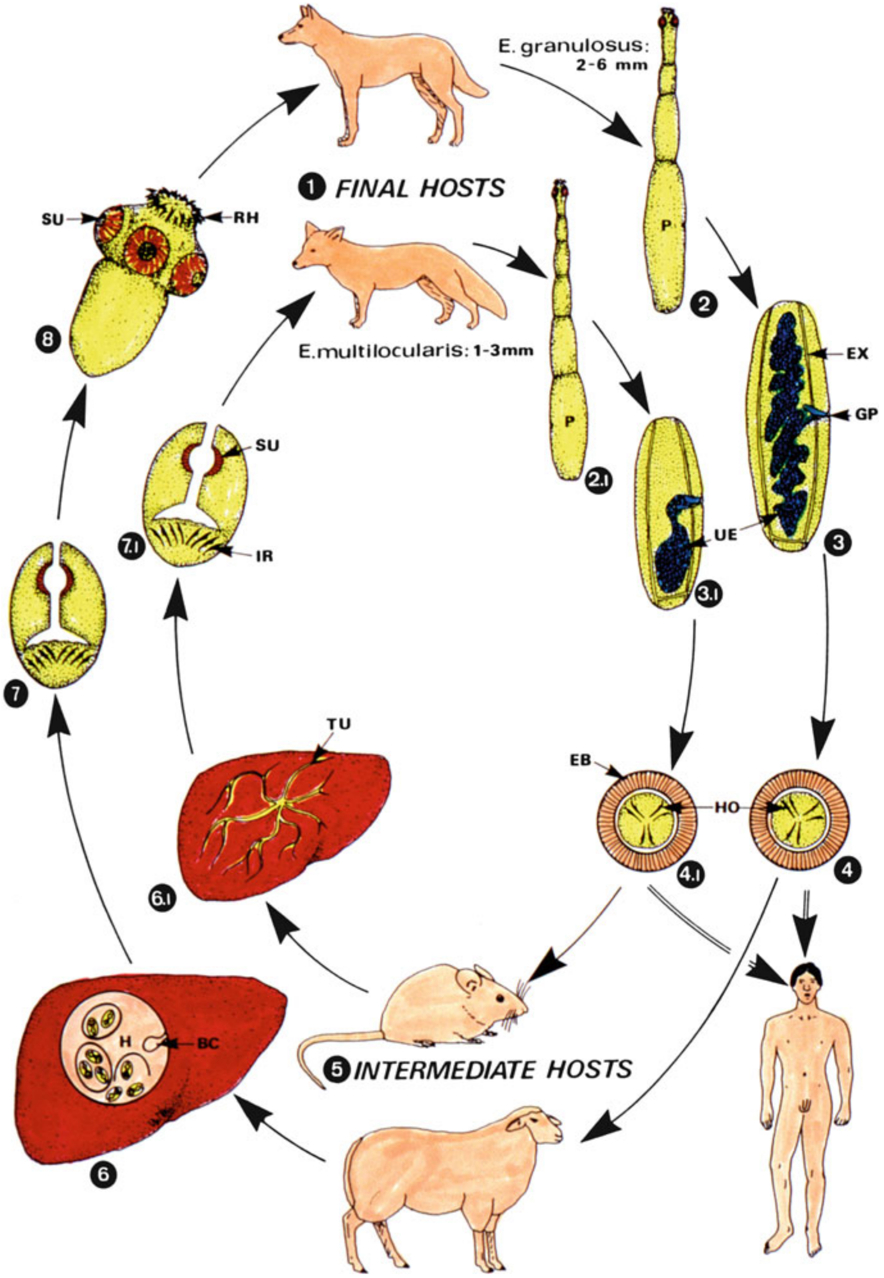
E. granulosus: 2-6 mm
① FINAL HOSTS
E.multilocularis: 1-3mm
SU
RH
⑧
P
②
P
②.1
EX
GP
SU
IR
⑦.1
UE
③
③.1
⑦
TU
EB
HO
④.1
④
⑥.1
H
BC
⑤ INTERMEDIATE HOSTS
⑥

Fig. 4.30 Life cycles of *Echinococcus granulosus* (**1–8**) and *E. multilocularis* (**1.1–7.1**). (**1**, **1.1**) Final hosts may be dog, cat or fox with clear, species-specific preference. (**2–3.1**) Adult worms, which live in the small intestine of the final host, may be differentiated according to the size of the terminal proglottids (P), shape of uterus (UE) and size of rostellar hooks. (**4**, **4.1**) Eggs containing an infectious oncosphaera larva are released from the detached drying proglottid in the feces of the host; eggs are indistinguishable from those of *Taenia* spp. (**5**, **5.1**). Eggs are orally ingested by intermediate hosts or man with contaminated food. (**6**, **6.1**) Inside the intestine of the intermediate

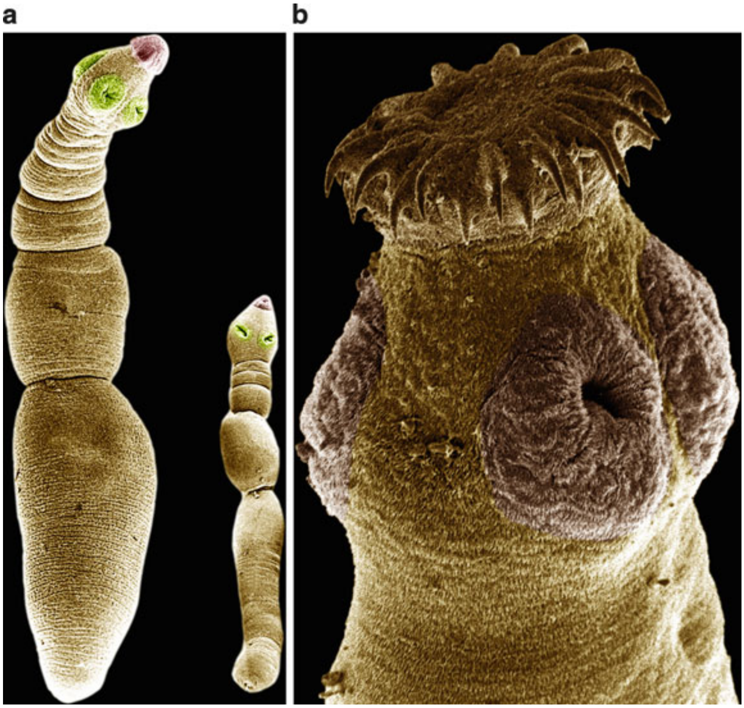

Fig. 4.31 Scanning electron micrographs. (**a**) Adult worms of *Echinococcus granulosus* (*left*) and *E. multilocularis* (*right*). (**b**) Scolex of *E. multilocularis* showing hooks and suckers

severely destructed (Fig. 4.32). The detailed life cycle of both species is depicted in Fig. 4.30.

Besides these two very important and widely spread *Echinococcus* species, several others have been described, which are listed in the Table 4.4.

Inside the intermediate hosts, typical cysts or cyst-like structures are formed by both *E. granulosus* and *E. multilocularis*. The origin is the same: An oncosphaera larva, which hatches from the egg inside the intestine of the

Fig. 4.30 (continued) hosts (including man) the oncosphaera hatches, enters the wall and may migrate (via blood) to many organs. Cysts are formed mostly in the liver and lung; in *E. granulosus* large unilocular hydatids occur, which are filled with fluid (containing thousands of protoscolices), whereas in *E. multilocularis* a tubular system infiltrates the whole organ (giving rise to alveolar aspects in sections). (**7**–**8.1**) In brood capsules of both cyst types protoscolices are formed, which may become evaginated (**8**) even inside their cysts. Evaginated or not, protoscolices are fully capable of infecting final hosts when they feed on infected organs of intermediate hosts. *BC* brood capsule, *EB* embryophore of the egg, *EX* excretory vessels, *GP* genital pore, *H* hydatid, *HO* hooks of oncosphaera, *IR* invaginated rostellar hooks, *P* proglottid, *RH* rostellar hooks, *SU* sucker, *TU* tubular system, *UE* uterus containing eggs

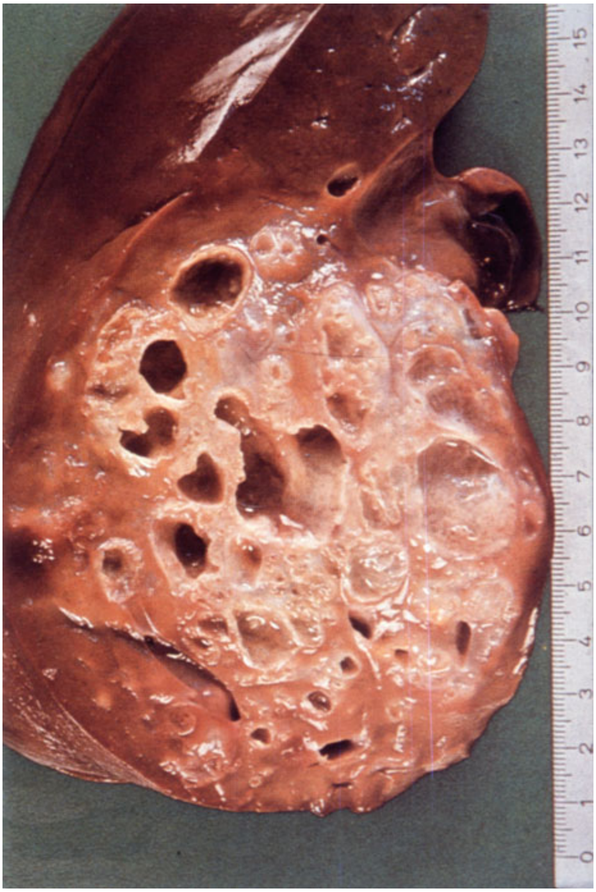

Fig. 4.32 Human liver showing the cross-sectioned hollow tubes of a cyst system due to an infection with *Echinococcus multilocularis*

intermediate host, penetrates into the wall of the intestine, reaches the blood vessel system and is transported by the help of the bloodstream to the final place (=mostly liver). There the cells inside the oncosphaera start an enormous asexual reproduction leading to large species-specific structures:

(a) **Hydatids** are formed in the case of *Echinococcus granulosus* infections (Table 4.3). These hydatids are large (up to 20 cm in diameter), fluid-filled bladders at the inner border of which smaller bladders are formed. Inside these “brood capsules”, so-called protoscolices are formed (Fig. 4.30). If a final host ingests such capsules or portions of them within meat of liver or lung, each protoscolex starts to develop into an adult worm (Fig. 4.31).

(b) **Twisted systems of empty (=non-fluid-filled) tubes** are produced inside intermediate hosts (Table 4.3) in the case of infections after ingestion of eggs of *E. multilocularis* and some related species (Table 4.3, Figs. 4.30 and 4.32). At the inner wall of these hollow tubes, protoscolices are

Table 4.3 Differentiation between the gravid specimens of *E. multilocularis* and *E. granulosus* (after Piekarski 1962)

Characteristics	*E. multilocularis*	*E. granulosus*
Length of the body	1.11–2.71 mm, average: 2.13 mm	2.10–5.02 mm, average: 3.36 mm
Length of the terminal segment	Smaller than half the whole length of the body: 0.44–1.11 mm, average: 0.85 mm	Usually longer than half the length of the whole body: 1.02–3.2 mm, average: 1.95 mm
Numbers of segments	3–5 (in dogs usually 4)	3
Sexually mature segment	The last but two	The penultimate one
Number of testes	14–31, average: 22	38–52, average: 44
Number of testes in front of the cirrus sac	0–5, average: 2	9–23, average: 15
Uterus of the gravid segment	Without lateral branches	Lateral branches usually distinct

Table 4.4 Further *Echinococcus* species

Species	Final hosts	Intermediate hosts, species	Intermediate hosts: parasitized organs
E. canadensis (EG)	Dogs, wolves	Cervids, **humans**)	Lung, liver; CE
E. equinus (EG)	Dogs	Horses, donkeys, zebras	Liver, CE
E. felidis (EG)	Lions	Warthogs	Liver, CE
E. intermedius (EG)	Dogs	Pigs, cattle, camels, goats, **humans**	Liver, lung, CE
E. ortleppi (EG)	Dogs	Cattle, buffalo, sheep, goat, **humans**	Lung, liver, CE
E. oligarthrus	Wild large cats (puma, jaguar)	Rodents, pacas, **humans**	Skin, muscles, inner organs, UE
E. shiquicus	Tibet fox	Pika (*Ochontona curzoni*)	Inner organs, no human cases known
E. vogeli	Forest dog (*Speothos venaticus*)	Rodents, **humans**	Liver, lung, other organs, PE

CE cystic echinococcosis, *PE* polycystic echinococcosis, *UE* unicystic echinococcosis

formed, which grow up to final adult worms as soon as final hosts have ingested these stages (Figs. 4.30 and 4.31a).

4. **Symptoms of the disease (Echinococcosis, Echinococciasis)**: The cysts grow rather slowly and are separated from the surrounded tissues by peculiar layers, so that the immune system of the host takes no or only little notice from the

growing cyst or tube-like system, respectively. Depending on the infested organ, clinical symptoms are different. In cases of liver infections, disturbances of digestion are noted as well as a pressure feeling in the liver region. In general also ascites production is common. In the case of lung stages, pleural fluids may introduce collapse of the lungs, while stages in the brain are characterized by severe symptoms like neuromotor deficiencies (e.g. paralyses). In the case the cysts occur inside bones, fractures are common. The rare cases of ocular infestations lead to a so-called exophthalmos—protruding eyes.

5. **Diagnosis**: The primary diagnosis in humans is based on the detection of cystic structures in different organs (liver, lung, brain, uterus, etc.). This can be done by the help of computer tomography, X-ray techniques, sonography, etc. These techniques do not allow a species-specific diagnosis. However, species determination is very important, since the fine tubular structures of *E. multilocularis* contain omnipotent cells, which would be spread, if such a structure is cut through during surgery. Then the included omnipotent cells would become able to produce further cyst-like structures in other organs. **Very important**: **Thus in no case—neither in cysts due to *E. granulosus* nor in the case of the presence of cyst-like tubes of *E. multilocularis*—probing excisions are allowed!** Some serologic methods, however, allow even species determination and thus are very important for preparations to remove the cysts or cyst-like structures from the infected organs by the help of surgical methods.
6. **Pathway of infection**: Oral by uptake of eggs from feces of final hosts (dogs, cats, foxes, etc.) or from the fur of these animals. **Attention**: These very small eggs can become washed out from the feces and transported by feet of animals or humans' shoes into households. Thus, it is recommended in regions with numerous foxes to clean feet of dogs and shoes of persons before entering the home.
7. **Prophylaxis**: Avoidance of contact with living or dead foxes, cats and dogs of unknown origin. Dogs and cats should be protected by regular application of antiworm compounds, which act as well against cestodes and nematodes. Hunters should always wear boots, which allow hot cleaning, and use one-way gloves when it is needed to investigate the fur of wild animals or when skinning foxes in order to get their fur.
8. **Incubation period**: Unknown, but surely many months.
9. **Prepatent period**: In intermediate hosts (inclusive humans), it takes surely long until first clear symptoms occur indicating an infection with *Echinococcus* cysts.
10. **Patency**: Years, lifelong if not removed.
11. **Therapy**: In the case of the bladder-like large cysts (hydatids) due to infections with *E. granulosus*, surgical removal is possible depending on the position of the cyst inside the infected organ, whereas in the case of *E. multilocularis* surgical removal is very difficult, since these stages end in very fine, practically invisible strands. In these cases, surgery would be a big mistake, since single undifferentiated cells would remain and—like in cancer—the cell divisions would go on. Thus, in the case of an alveolar echinococcosis an operative

healing is practically excluded. In cases of inoperability a permanent daily chemotherapy using **albendazole** (12–15 mg/kg bodyweight) or **mebendazole** (50–60 mg/kg bodyweight) led to good survival rates. Also in cases of the successful removal of a hydatid cyst, it is recommended to go on with the drug application for at least 2 years.

Further Reading

Boufana B et al (2015) Canine echinococcosis: genetic diversity of *Echinococcus granulosus*. J Helminthol 89:689–698

Craig P et al (2015) *Echinococcus granulosus*: epidemiology and state-of-the-art diagnostics in animals. Vet Parasitol 213:132–148

Eckert J, Deplazes P (2004) Biological, epidemiological and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clin Microbiol Rev 17:107–135

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Gottstein B et al (2015) Threat of alveolar echinococcosis to public health – a challenge for Europe. Trends Parasitol 31:407–412

Knapp J et al (2015) Taxonomy, phylogeny and molecular epidemiology of *Echinococcus multilocularis*. Vet Parasitol 213:85–91

Manzano-Roman R et al (2015) Serological diagnosis and follow-up of human cystic echinococcosis: a new hope for the future. Bio Med Int, Article 428205

Mehlhorn H et al (1983) Proliferation and metastases formation of larval *Echinococcus multilocularis*. Parasitol Res 69:749–763

Oudni-Mirad M et al (2015) First molecular evidence of the simultaneous human infection with two species of *Echinococcus granulosus*. Parasitol Res. doi:10.1007/s0043-015-4836-x

Romig T et al (2015) Taxonomy and molecular epidemiology of *Echinococcus granulosus*. Vet Parasitol 213:76–84

Saarma U et al (2009) A novel phylogeny for the genus *Echinococcus*. Parasitology 55:87–90

Thompson RC (2008) The taxonomy, phylogeny and transmission. Exp Parasitol 119:439–446

4.3.6 *Dipylidium caninum*

1. **Name**: Greek: *di* = two, double; *pyle* = opening. Latin: *canis* = dog. English: Cucumber seed tapeworm; rice seed tapeworm. The Latin name of the worm was given describing the fact that both sides of the proglottids have a genital opening.

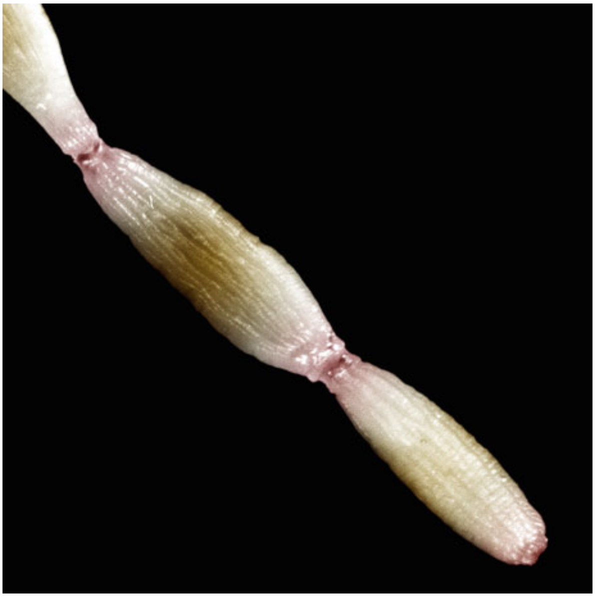

Fig. 4.33 Light micrograph of three terminal proglottids of *Dipylidium caninum*

2. **Geographic distribution/epidemiology**: Worldwide, common among dogs and cats—therefore increased transmission risks for holders of dogs and cats exist.
3. **Biology, morphology**: *D. caninum* parasitizes as adult worm mainly in dogs and cats and only rather seldom in humans (Figs. 4.26 and 4.33). It reaches a length of 20–70 cm and a width of 3–4 mm. The scolex is 0.5 mm wide, has a rostellum with 3–5 rows of small (7 μm) and large (13 μm) hooks and is provided with four suckers. Each proglottid includes two sets of male and female sexual organs, which are situated opposite to each other at the lateral sites possessing separate excretion channels. The terminal proglottids (Fig. 4.33) reach a length of 8–20 mm and are closely filled with 120 × 200 μm sized egg packages containing 8–18 eggs (mean 20) with diameters of about 30–50 μm (Fig. 4.27e). These thin-walled eggs contain the infectious 6-hook larva (oncosphaera). The shape of the whitish terminal proglottids is similar to cucumber seeds. Thus, this tapeworm got its trivial name “cucumber tapeworm”. Due to heavy contractions, these proglottids are able to creep around the anus and inside the fur of dogs and cats. During these movements, the typical egg packages were pressed out from the proglottids and thus they may become ingested by intermediate hosts such as flea larvae or mallophages. Inside the body cavity of these insects, the **oncosphaera** larva is transformed into the infectious **cysticercoid** larva, which grows up into the adult worm, as soon as the intermediate host is ingested by a final host. This need to ingest flea larvae or at least portions of them shows that with respect to humans mainly children become infected when playing with dogs and cats. After ingestion of

such cysticercoid larvae, it takes about 3 weeks until these stages are grown up into fertile adult tapeworms inside their final hosts.

Besides *D. caninum*, other species have the same type of life cycle: *D. sexcoronatum*, *Diplophylidium acanthotetra* and *D. noelleri* as well as several *Joyeuxiella* species.

4. **Symptoms of the disease (Dipylidiasis)**: In the case of low-grade infections, the symptoms of disease are unspecific. However, as soon as 100–200 adult worms are present inside a host bloody-slimy diarrhoea may occur accompanied by cramps. In addition, signs of urticarial, loss of bodyweight and blood eosinophilia were reported.
5. **Diagnosis**: Feces contain whitish-reddish appearing proglottids, which may reach in fresh feces a length of up to 1.5 cm (Fig. 4.33), but which appear after drying rice-grain-like, e.g., in underwear. In addition, infected persons may show a slight eosinophilia. Heavily infected children may be hit by restlessness due to itching along the anus region initiated by creeping proglottids. Infected dogs in households show sledging movements due to anal itching. Microscopical investigation of the feces reveals the typical egg packages (Fig. 4.27).
6. **Pathway of infection**: Oral by uptake of portions of fleas, flea larvae or mallophages containing the infectious cysticercoid larvae while playing with infected dogs or cats.
7. **Prophylaxis**: In the case of cats or dogs in households, these animals must regularly become dewormed at fixed intervals and kept free from fleas; the latter should be done by application of insecticides or repellents onto the body and on the floor.
8. **Incubation period**: 10–25 days.
9. **Prepatent period**: 18–25 days.
10. **Patency**: Up to one year (however, for dogs and cats remains the danger of repeated self-infections by uptake of infected insects.
11. **Therapy**: For humans, see *Taenia solium*; in the case of dogs and cats: use of praziquantel and treatment with insecticides in addition to use of repellents.

Further Reading

Beugnet F et al (2013) Preventive efficacy of Frontline® Combo and Certifed® against *Dipylidium caninum* infestation of cats and dogs using a natural flea infestation model. Parasite 20. doi:10.1051/parasite/2013006

Beugnet F et al (2014) Occurrence of *Dipylidium caninum* in fleas from client-owned cats and dogs. Vet Parasitol 205:300–306

4.3.7 Rare Tapeworms in the Intestine of Humans

***Mesocestoides* Species**

About 40 reports are available on infections of humans with worms of this genus (f.e. Chandler 1942; Ohtomo et al. 1983). Many cases remain unreported and therefore the data collected do not necessarily give the full picture of the situation. The final hosts of the worms are normally foxes and dogs, while amphibia, birds and/or mammals may be used as intermediate hosts. The mature worms are 40 cm × 2 mm in size. The infection of humans may occur via ingestion of the infectious so-called tetrathyridium larvae in raw meat originating from intermediate hosts. Symptoms of the disease are anorexia, abdominal pain and slight anaemia.

Further Reading

Boyce W et al (2011) Survival analysis of dogs diagnosed with peritoneal larval cestodiasis (*Mesocestoides* spp.). Vet Parasitol 180:256–261

Chandler AC (1942) First case of human infection with *Mesocestoides*. Science 96:112

Ohtomo K et al (1983) Therapeutic effect of paromomycin sulfate in the 13th case of *Mesocestoides lineatus* infection found in Japan. Jpn J Antibiot 36:632–637

Szell Z et al (2015) Environmental determinants of the spatial distribution of *Mesocestoides* spp. and sensitivity of flotation method for the diagnosis of mesocestoidosis. Vet Parasitol 212:422–430

Zalesny G, Hildebrand J (2012) Molecular identification of *Mesocestoides* sp. from intermediate hosts (rodents). Parasitol Res 110:1055–1061

Hymenolepis diminuta

This tapeworm of rats occurs worldwide. It reaches a length of 0.5 m. Its obligatory intermediate hosts are arthropods (fleas, mealworm beetles). The symptoms of the disease are low grade. For life cycle and therapy, see *H. nana* (Sect. 4.3.4).

Further Reading

D’Ovidio D et al (2015) Survey of *Hymenolepis* spp. in pet rodents in Italy. Parasitol Res 114:4381–4384.

Hamid MMA et al (2015) The prevalence of *Hymenolepis nana* among preschool children. Travel Med Infect Dis 13:172–177

Kim BJ et al (2014) Heavy *Hymenolepis nana* infection possibly through organic foods. Korean J Parasitol 1:85–87

Raillietina celebensis

This tapeworm uses rats as final host and insects as intermediate host. That is why often children are infected by contact with dogs or cats. They may take up the larvae by oral ingestion of portions of infected fleas. The excreted proglottids are very short (3 mm) and appear like rice grains. This worm is endemic in South-East Asia and South America.

Further Reading

El-Bahy NM, Bazh EKA (2015) Anthelmintic activity of ginger, curcumin and praziquantel against *Raillietina cesticillus*. Parasitol Res 114:2427–2434

Jyrwa RDB et al (2014) Molecular characterization of the Indian poultry nodular tapeworm *Raillietina echinobothrida*. J Parasit Dis 38:22–26

Inermicapsifer madagscariensis

In Africa, this tapeworm can be found mostly in rodents as final hosts, but in general not often in humans. However, in Cuba the worm often occurs in small children, whose feces then are covered with proglottids appearing like rice grains, being 3 mm in size. The most common clinical symptom is abdominal pain. The exact way of infection is unknown.

Further Reading

Numez G et al (1996) Infection by *Inermicapsifer madagascariensis*. Rev Cubana Med Trop 48:224–226

Schmidt GD, Wertheim G (1988) *Inermicapsifer beveridgei* n. sp. J Parasitol 74:487–488

***Bertiella* Species (e.g. *B. studierii*)**

This worm was found mostly in monkeys, but also rarely in humans in Asia. A few further cases are described worldwide too, based on excreted proglottids.

Chemotherapy of Rare Tapeworms

In the case of these rare tapeworms, praziquantel was again the medication of choice; for dosage, see *Taenia solium* (Sect. 4.3.1).

4.3.8 *Cysticercus* Species (Cysticerciasis)

1. **Name**: Greek: *kystos* = cyst; *kerkos* = tail. Latin: *cellula* = small cell, membranous structure.
2. **Geographic distribution/epidemiology**: Worldwide, especially in Latin America, Africa, China and India; worm stages were found in 2–3 % of the autopsies in certain countries.
3. **Biology, morphology**: *Cysticercus cellulosae* is the larva of the tapeworm *Taenia solium*, which normally lives as an adult worm (Figs. 4.22, 4.23 and 4.24) in the intestine of humans as final hosts and can be found as cysticercus larva in pigs as intermediate hosts. *Cysticercus cellulosae* appears histologically as a liquid-filled bladder of 1–2 cm in diameter. In its interior, the scolex of the later adult tapeworm (with its typical ring of hooks) develops out of a germinal layer. Cysticerci in humans are caused by the consumption of tapeworm eggs originating from own or foreign feces. In the human intestine, the oncosphaera hatches from the egg and penetrates into the intestinal wall. Via blood vessels the larva may reach practically all organs that are well supplied

with blood. The fully functional cysticercus with its inserted scolex is produced within 8–10 weeks in the interstitium. In this case, humans have become the intermediate host. Sometimes also lateral growth occurs with formation of larger protrusion. This type of a cyst stage was named *Cysticercus racemosae* by the German physician Virchow (1821–1902).

4. **Symptoms of the disease (Cysticercosis)**: The incubation time is 8–10 weeks. Depending on the parasitized organs and the number of the cysticerci occurring, some symptoms can be fatal (e.g. in cases of brain infection). If muscles are infected, muscle pain and paralysis arises, especially as soon as the cysticerci calcify and thereby induce pressure on nerves. The cysticercosis of the brain can remain undetected for a long time despite of the existence of numerous cysts. In other cases, motor or sensory deficiencies may occur as well as sensory disorders, depending on the location of the cysts in the brain. Also symptoms such as psychic abnormal behaviour and speech disorders a.s.o. have been observed. In the case of interrupted fluid flow in the brain, intracranial pressure symptoms can occur. Frequently cramps occur as first sign of the disease. Cysticerci situated in the spinal cord lead to deficits in the sensory system and may end finally in paraplegia symptoms. If eyes are afflicted, exophthalmus and strong visual defects are introduced.
5. **Diagnosis**: By the help of computer tomography or magnetic resonance imaging of the crane, it can be diagnosed whether a neurocysticercosis has been induced. Ocular cysticercosis can be proven by examination of the anterior and posterior chamber of the eye. The diagnosis can be double checked by the determination of specific antibodies in the fluid and blood serum (by the help of ELISA and other techniques). In most cases, existing cross reactions with echinococcosis or other helminthiasis can be differentiated by the help of Western blot. False-negative results occurred in 10–35 % of the cases. However, even in the case of negative immunodiagnostic results a therapeutic treatment (trial) can be reasonable if a cysticercosis is suspected. In biopsates or in tissues obtained during surgical operations, the typical germinal epithelium or the invaginated scolex may be detected.
6. **Pathway of infection**: Orally by ingestion of tapeworm eggs originating from human feces. Autoinfection is possible, if after chemotherapy the adult tapeworm remains too long in the intestine of the patient. If this happens, the terminal proglottids are digested, the eggs are released in the intestine and the hatched oncosphaera larvae may immediately penetrate the intestine wall, thus reaching the blood vessels and becoming potentially distributed inside the whole body.
7. **Prophylaxis**: Avoiding contact with potential accumulations of human feces close to open latrines, parking places and wild camping grounds a.s.o. **Caution**: Tapeworm eggs may survive for at least 60 days at temperatures higher than 0 °C. Even temperatures beyond 0 °C will be sustained for a short period of time. Repetitive infections are possible, since immunity is not developed.
8. **Incubation period**: 8–10 weeks.

9. **Prepatent period**: About 8 weeks after the infection, the cysticercus has reached a well notable size.
10. **Patency**: 2 years at least.
11. **Therapy**: Albendazole (15 mg/kg bodyweight daily for a period of 8 days) is the medication of choice. Praziquantel (50 mg/kg bodyweight daily for a period of 15 days) is effective as well. In the case of a neurocysticercosis, corticosteroids can increase adverse reactions during the therapy (due to setting free of foreign proteins). If treatment fails and in the case of a hydrocephalus internus and very large ventricular cysts, a neurochirurgical surgery cannot be avoided.

Further Reading

Del Brutto OH, Garcia HH (2015) *Taenia solium* cysticercosis: the lessons history. J Neurol Sci

Garcia HH et al (2014) Immunology *Taenia solium* taeniasis and human cysticercosis. Parasite Immunol 36:388–390

Garcia HH et al (2014) Clinical symptoms, diagnosis and treatment of neurocysticercosis. Lancet Neurol 13:1202–1215

Rasamoelina-Andriamanivo H et al (2013) Control of cysticercosis in Madagascar. Trends Parasitol 29:538–546

4.3.9 *Coenurus* Species

1. **Name**: Greek: *koinos* = together; *ura* = tail.
2. **Geographic distribution/epidemiology**: Worldwide in countries, where large numbers of dogs are kept; however, in general humans are rarely infected.
3. **Biology, morphology**: The item *coenurus* refers to tapeworm larvae of the genus *Multiceps*, which can grow up to the size of an apple. As adults these worms settle in the intestine of dogs (final hosts) and as larvae they normally live in the brain of herbivores (e.g. sheep). Infection of humans is relatively rare. Characteristic of the *coenurus* is that the proliferation of the protoscolices occurs at the inner side of the transparent cyst wall and that they are not included in separate small capsules.
4. **Symptoms of the disease**: In the case of an infection of the brain neurological deficiencies occur (**whirling disease** in sheep) and paralysis. Also other symptoms occur which are often relatively unspecific but resemble infections with *Echinococcus* stages. In the case of an infection of the eye, an extreme exophthalmos with specific damages may occur like in the case of *Echinococcus*.
5. **Diagnosis**: Cysts are mostly occasionally detected in connection with a CAT scan (computed tomography) which is done for other reasons.

6. **Pathway of infection**: Orally by ingestion of eggs of the tapeworm *Multiceps multiceps* (originating from dog feces). Many of the infected humans have apparently a predisposition, since the number of the infected humans is very low compared with the high distribution rate of the tapeworm among dogs.
7. **Prophylaxis**: Cleanliness and caution when dealing with foreign dogs and their feces.
8. **Incubation period**: Unknown.
9. **Prepatent period**: Infected humans do not excrete eggs or other transmittable stages.
10. **Patency**: Years.
11. **Therapy**: The medication of choice is praziquantel in dosages like those used in the case of neurocysticercosis, which, however, must always become accomplished by the administration of antihistamines.

Further Reading

Haridy M et al (2013) *Coenurus cerebralis* cysts in the left lateral cerebral ventricle of a ewe. J Vet Med Sci 75:1643–1646

Madhu DN et al (2014) *Coenurus gaigeri* cyst in the thigh of a goat and its successful management. J Parasit Dis 38:286–288

Rostami S et al (2013) Cytochrome c oxidase subunit 1 and 12S ribosomal RNA characterization of *Coenurus cerebralis* from sheep in Iran. Vet Parasitol 187:141–151

4.4 Nematodes (Nematozoa, Roundworms)

Greek: *nema* = filament; *zoon* = animal. English: round worms.

Nematodes have depending on the species a cylindrical or filament-like body shape. They mostly are sexually differentiated in males and females, which in their largest numbers of species are free living in the soil or in fresh or salt waters. However, also many species have developed a parasitic life cycle in humans, animals and plants. Their systematic position is in many details still under discussion.

According to their recent taxonomy status the nematodes and their subdivision into classes is based on the presence and absence of caudal, even in the microscope only hardly visible sensory organs (the so-called **phasmids**) and their ability to become attached by the help of secretions of caudal glands at surfaces. Furthermore, the taxonomy uses criteria like the shape of the oesophagus, which are often hardly detectable. Thus, the systematic used here in this book and the details shown here consider mainly the morphology and life cycles of the nematodes.

Phylum: NEMATHELMINTHES (selected extract)
Subphylum: Nematoda
Class: Adenophorea (Aphasmidea)
Order: Enoplida
Family: Trichuridae (Trichurinae, Capillariinae)
Family: Trichinellidae
Family: Dioctophymatidae
Order: Mermithida
Family: Mermithidae
Class: Secernentea (Phasmidea)
Order: Rhabditia
Family: Rhabditidae
Family: Strongyloididae
Order: Strongylida
Superfamily: Ancylostomatodea
Family: Ancylostomatidae
Family: Uncinariidae
Superfamily: Trichostrongyloidea
Family: Trichostrongylidae
Family: Dictyocaulidae
Family: Heligmosomatidae
Superfamily: Metastrongyloidea
Family: Metastrongylidae
Family: Angiostrongylidae
Family:Protostrongylidae
Superfamily: Strongyloidea
Family: Strongyloidae
Order: Ascaridida
Superfamily: Ascaridoidea
Family: Ascarididae
Family: Toxocaridae
Family: Anisakidae
Family: Cosmocercidae
Superfamily: Oxyuroidea
Family: Oxyuridae
Superfamily: Heterakoidea
Family: Heterakidae
Family: Ascaridiidae
Order: Spirurida
Superfamily: Spiruroidea
Family: Spiruridae
Family: Spirocercidae
Superfamily: Physalopteroidea
Family: Gnathostomatidae
Family: Physalopteridae

(continued)

Superfamily: Filarioidea
Family: Filariidae
Family: Onchocercidae
Order: Camallanida
Superfamily: Camallanoidea
Family: Camallanidae
Superfamily: Dracunculoidea
Family: Dracunculidae
Family: Philometridae
Family: Micropleuridae
Family: Anguillicolidae
Order: Diplogasterida
Order: Aphelenchida
Order: Tylenchida
Superfamily: Sphaerularioidea
Family: Sphaerulariidae

Table 4.5 Zoonotic infections of humans by important nematodes

Species	Nonhuman hosts	Observations in humans
Ascaris suum	Pigs	Mature adults in small intestine
Ancylostoma braziliense	Cats, dogs	Cutaneous larva migrans
Ancylostoma caninum	Dogs	Adults, cutaneous larva migrans
A. ceylonicum	Cats, dogs	Adults
A. japonica	?	Larva migrans
A. malayanum	Bears	Larva migrans
A. tubaeforme	Cats	Larva migrans
Necator suillus	Pigs	Adults
Trichuris suis	Pigs	Adults
Trichuris vulpis	Foxes, dogs	Adults

Zoonotic Infections: Nematodes

Nematodes are very common parasites of humans (Table 4.5). Especially due to the fact that besides specialists, which like *Ascaris lumbricoides* mainly infect humans, also many species of animals may also infect humans, thus inducing zoonosis (Table 4.6).

Further Reading

Chan MS (1997) The global burden of intestinal nematode infections – fifty years on. Parasitol Today 13: 439–443

Coombs I, Cromptom DTW (1991) A guide to human helminths. Taylor and Francis, London

Holland CV (2005) Gastrointestinal nematodes: *Ascaris*, hookworms, *Trichuris* and *Enterobius*. In: Cox FEG et al (eds) Parasitology. Hodder Arnold, Washington, DC

Table 4.6 Infection rates of humans due to common species of nematodes and morbidity (estimates) according to Holland (2005)

Features	*Ascaris*	*Ancylostoma*	*Necator*	*Trichuris*
Number of subspecies	16	23	8	71
Species infecting humans	2	7	3	3
Global no. of infection	1470×10^6	135×10^6	735×10^6	1300×10^6
Estimated cases of morbidity	$120–215 \times 10^6$	$27–39 \times 10^6$	$63–91 \times 10^6$	$90–130 \times 10^6$

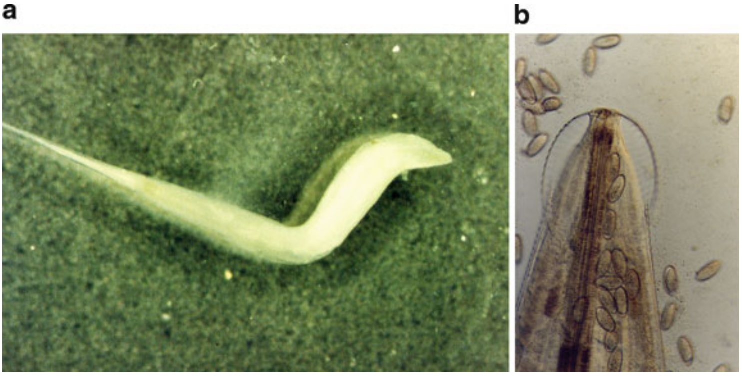

Fig. 4.34 Light micrographs of adult female worms: (**a**) Total aspect, note the spiky terminal end. (**b**) Anterior end showing a bulbous-like structure at the very tip of the worm and a series of excreted eggs

4.4.1 *Enterobius vermicularis* (Enterobiasis)

1. **Name**: Greek: *enteron* = intestine; *bios* = life. Latin: *vermicularis* = worm like. Greek: *oxys* = quick; *ura* = tail. English: Pin worm.
2. **Geographic distribution/epidemiology**: Worldwide about 1.5 billion of humans are infected. Thus, this worm is besides *Ascaris lumbricoides* (human roundworm) one of the most common human parasites.
3. **Biology, morphology**: The whitish appearing adult females reach a length of up to 1 cm (Fig. 4.34a, b), parasitize in the lumen of the colon and rectum and are characterized by their long but small posterior end, which led to the trivial name "pin worm". The males are only 2–5 mm long, have no pointed posterior end and die rather quickly after copulation with a female. Thus, they are often seen on the surface of human feces. The females leave during night (=during the rest of the infected person) the anus and glue their fertilized eggs (Fig. 4.35) at the perianal skin. Due to this fact, the eggs are rather seldom seen in the feces and thus an infection with *E. vermicularis* remains often undetected. Therefore, in order to diagnose such an infection it is needed that in the morning the anus of a possibly infected person has to be touched by the help of a transparent

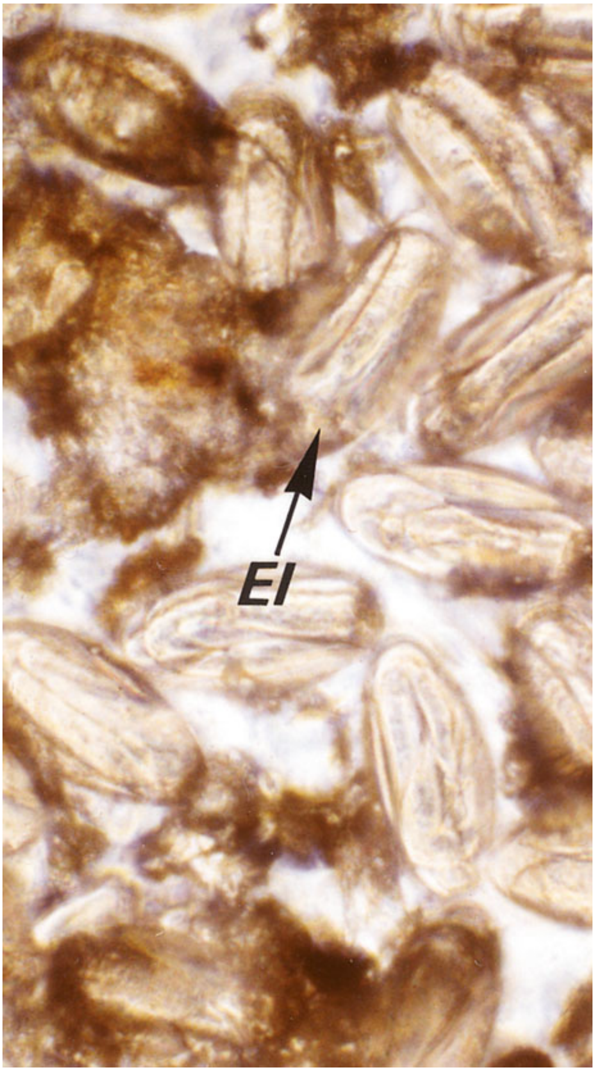

Fig. 4.35 Light micrograph of *Enterobius vermicularis* eggs on a transparent gluing tape. Note that already larvae are present inside the eggs (EI)

gluing plastic strip. Microscopical inspection then will show the thin-walled eggs, inside which mostly already within 5 h the infectious larva will develop. The first infection of a person starts by oral uptake of eggs of a foreign person, e.g. by contact to contaminated toilets or door grips, while further infections are mostly self-infections, which make treatment difficult.

4. **Symptoms of the disease** (**Enterobiasis**): In most of the cases, nightly itching around the anus occurs, which leads to sleeplessness (insomnia) and restlessness. In the case of female patients, also infections of the urogenital system had been reported, which were detected by occurrence of intense itching. Only in

very rare cases, direct symptoms of disease occurred such as abdominal pain, diarrhoea, cramps, etc.

5. **Diagnosis**: Patients claiming the above cited itching symptoms should be asked to visit the physician without cleaning the anal region. Then a test using the above-described gluing tape will show by the help of light microscopy the typical thin-walled eggs measuring 50–60 μm by 20–30 μm, which appear suppressed at one longitudinal side (Fig. 4.35). Also dead male and motile whitish females may be detected.
6. **Pathway of infection**: Oral by uptake of eggs containing larvae. This may occur by self-infections (hand-mouth) or when touching egg-contaminated toilets or door grips.
7. **Prophylaxis**: In cases of enterobiasis in a family or in a kindergarten, intense handwashing and hot water cleaning of toilets should be done. Medication of the whole family is needed as well as hot washing of the underwear of treated persons.
8. **Incubation period**: 1–4 weeks.
9. **Prepatent period**: 5–10 weeks.
10. **Patency**: Eventually years due to repeated self-infections. However, a single female lives only 3–4 months.
11. **Therapy**: Single dosages of mebendazole (100 mg), albendazole (200–400 mg (children below 2 years: 15 mg/kg bodyweight) and other anthelmintics like pyrvinium or pyrantel are effective. However, due to autoinfections or reinfections a repetition of the treatment after 2–3 weeks is necessary. Furthermore, it is known that the relevant medical devices have less good effects on the early stages after hatching of the larva from the egg. In cases of families, it is often needed to treat the whole family at the same time, since slight infections may be hidden and will become sources of reinfections of treated persons. Thus, in peculiar cases up to 5–6 courses of treatment may be needed.

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4.4.2 *Ascaris lumbricoides* (Ascariasis)

1. **Name**: Greek: *ascaris* = intestinal worm. Latin: *lumbricoides* = like *lumbricus* = earth or rain worm. English: Human roundworm.
2. **Geographic distribution/epidemiology**: Worldwide at least 1.5 billion humans are infected.
3. **Biology, morphology**: The adult yellowish-white *Ascaris* worms, which may reach a considerable length (males: 10–30 cm; females: 22–52 cm), by a width of about 0.6–0.8 cm, parasitize mainly in the small intestine of humans, monkeys and apparently also in bears (Figs. 4.36 and 4.37a). They are characterized by their anterior three-lipped head capsule, the inner borders of which being equipped with fine teeth (Fig. 4.37b). The females can lay up to 200,000 eggs a day for a rather long period (up to 1 year, only rarely longer). These eggs, which have a yellowish-brown and sculptured surface, are broadly oval and measure when fertilized about 60 μm in length, but their shape may vary. As seen by the help of the microscope the freshly laid egg contains only

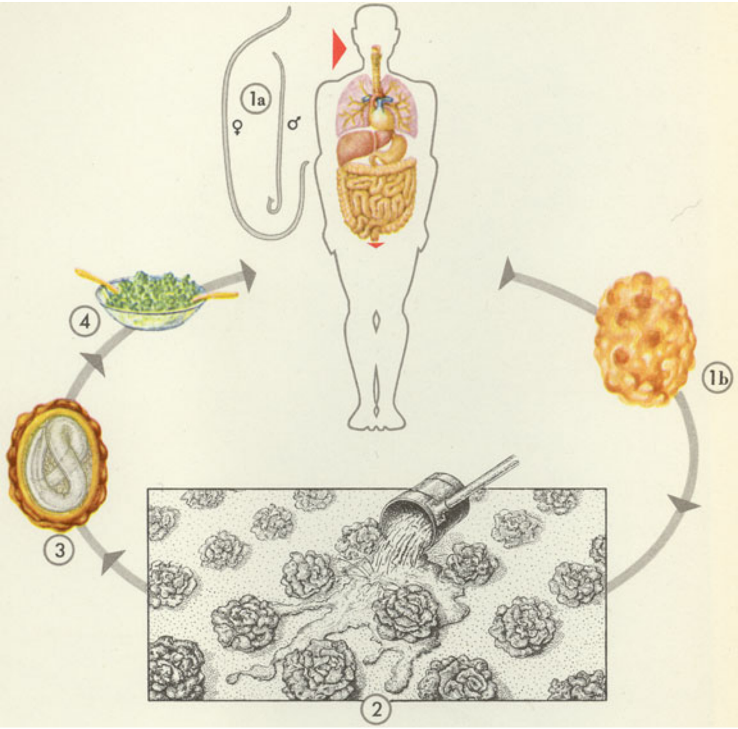

Fig. 4.36 Diagrammatic representation of the life cycle of *Ascaris lumbricoides* (after Piekarski 1962). (**1a**) Adult worms (♀♂). (**2**) Eggs are distributed on plants using fecally contaminated water. (**3**) Egg containing an infectious larva. (**4**) Infection by ingestion of contaminated (undercooked or not washed) food

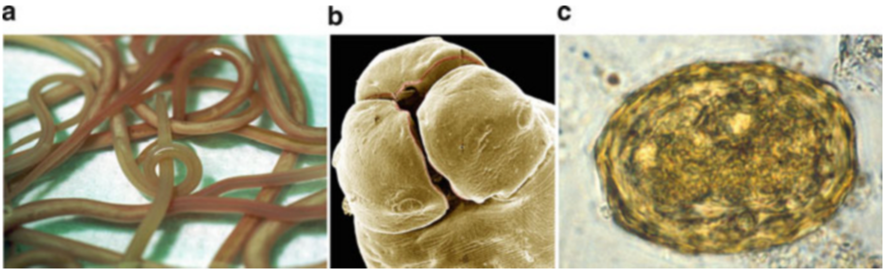

Fig. 4.37 (**a**) Light micrograph of excreted adult *Ascaris lumbricoides* after drug treatment. (**b**) Scanning electron micrograph of the anterior end (mouth region) showing the typical three lips with tiny teeth at the borders. (**c**) Light micrograph of an egg of *Ascaris lumbricoides*, which according to its size should be fertilized

the egg cell. Outside of the body under influence of oxygen the formation of the larva 1 is started, which moults into the infectious larva 2. This process is temperature dependent and thus needs 8–50 days. The **infection of humans** occurs by oral uptake of such larva-containing eggs (Fig. 4.37c). Inside the intestine, the larva 2 is set free from the egg shell, enters the intestinal wall and reaches within blood vessels the liver, where another moult leads to the formation of larva 3 (=the wandering stage). These larvae 3 reach after heart passage the lungs, where they stay for about 14 days. Then they migrate via trachea and oesophagus into the small intestine, where they reach after two more moults within 45–60 days fertility. The females start copulation with males and lay eggs for about 1 year. This seems short; however, they produce during this period about 60 million eggs. Some females may enter (mostly at night during sleep of the infected person) the stomach and creep up the oesophagus into the mouth and are occasionally expectorated. Other adults penetrate into the intestinal wall and enter finally the peritoneal cavity; others penetrate eventually into the liver, leading in both cases to severe complications.

The larvae of the species of the pig (*Ascaris suum*) may enter the human body, but do not reach maturity in all cases. Leles et al. (2012) found indications that *A. suum* is identical to *A. lumbricoides*.

4. **Symptoms of the disease (Ascariasis)**: This worm species, which belongs to the most common worms infecting humans, may remain harmless, but also introduce severe diseases or even death (it is reported by WHO that at least 12,000 persons die per year due to complications during an *Ascaris* infection). In general, the following symptoms may occur:
   (a) **During passage of the lung**:
   Eosinophilic lung infiltrations (eventually visible during X-ray examination), fever and eventually pneumonia.
   (b) **Intestinal phase**:
   Abdominal pain, vomiting, enteritis, danger of blockage of the intestine (*ileus verminosus*), in the case of entering the peritoneum peritonitis may occur; the blood status shows an eosinophilia. Occasionally, the *Ascaris*

stages may enter and block the excretion channels of the gall. Also unspecific symptoms may occur such as restlessness and insomnia.

5. **Diagnosis**: Infections with *A. lumbricoides* are most easily diagnosed by the use of enrichment methods such as S.A.F. or M.I.F., which show the typical eggs (Fig. 4.37). According to early microscopical reports fertilized eggs measure 60–70 μm in length, while non-fertilized ones should measure 90 × 50 μm. If only the slender type of eggs is found, apparently only one or several females are present inside the intestine of this patient. Occasionally, old worms are found in the feces, others might be expectorated during sleeping and again others enter the bile ducts. The latter can be diagnosed using sonography or X-ray observation. During lung passage, larvae may also occur in the saliva after coughing. A typical sign for wandering larva inside the lung is the high-grade eosinophilia in blood.
6. **Pathway of infection**: Oral when ingesting eggs containing the infectious larvae. This may occur when salad or fruits are fecally contaminated. Since an infection does not introduce immunity, repeated infections may occur, thus increasing the worm load of a person.
7. **Prophylaxis**: Washing of salad and plants before eating; attention at potentially contaminated toilets (handwashing is strongly recommended); cleaning shoes after visit of unclean foreign/field toilets.
8. **Incubation period**: The first unspecific symptoms (coughing, allergic reactions) may occur already during the first larval wandering phase (i.e. 7 days after the oral uptake of eggs). However, about 80 % of low-grade infected persons remain symptomless.
9. **Prepatent period**: 2–3 months.
10. **Patency**: About 1 year.
11. **Therapy**: Drugs of choice are **mebendazole** (2 × 100 mg daily for 3 days) and **albendazole** (1 × 400 mg adults; children below 2 years: 1 × 15 mg/kg bodyweight). Other anthelmintics such as piperazine, levamisole, pyrantel or fenbendazole are also effective. In the case of intestinal obstruction by massive amounts of worms, a chirurgical intervention is needed. In the case of an invasion of the bile ducts, an endoscopical extraction can be tried before surgery.

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4.4.3 *Trichuris trichiura* (Trichuriasis)

1. **Name**: Greek: *thrix*, *trichos* = hair; *ura* = tail. English: Human whipworm.
2. **Geographic distribution/epidemiology**: Worldwide about 600–800 million people are infected.
3. **Biology, morphology**: The adult, whitish appearing worms (Fig. 4.38a) reach in both sexes a length of about 5 cm and parasitize in the mucous layer of the caecum and colon of humans. They are characterized by a very long anterior region, which is much thinner than the posterior part, thus leading to the aspect of a whip. The very tip of the mouth region is extremely tiny so that the worm can even enter it into single cells. The eggs (Fig. 4.38b) reach a size of 50 μm × 25 μm and have a very typical appearance due to their plug-like poles and their clear to dark brown colour. They can hardly become confused with the eggs of other genera of nematodes. These eggs are excreted unembryonated and the development of the larva is temperature dependent. Thus, it takes 4–6 months at 15 °C, 3–4 weeks at 26 °C and only 11 days at 35 °C. The **infection** occurs when humans ingest larva-containing eggs with fecally contaminated food. After hatching inside the small intestine the larvae pass, without any special migration route, directly into the large intestine, where they become sexually mature within 1–3 months. The eggs of this worm may remain infectious for years outside of a body.
4. **Symptoms of the disease (Trichuriasis)**: Infections with a low number of worms remain mostly symptomless and thus are not discovered. However, infections with huge numbers of worms—mostly common in the tropics—may induce slimy-bloody diarrhoeas, anaemia, colitis and in rare cases rectum prolapse. The blood picture of such patients shows mostly a middle-grade eosinophilia.
5. **Diagnosis**: Concentration methods (M.I.F., S.A.F.) deliver the typical bipolar, 50 × 25 μm sized eggs, when examined by light microscopy (Fig. 4.38b).

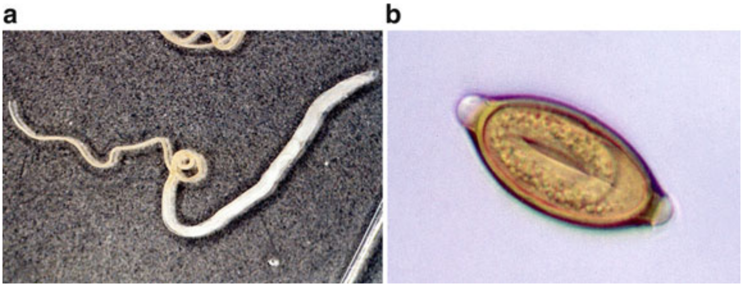

Fig. 4.38 *Trichuris trichiura*. (**a**) Macrophoto of an adult worm. In former times it was thought that the *thick* portion would be the anterior end, thus resembling a grip of a whip. This idea was name giving. (**b**) Light micrograph of an egg within which the larva is already developed. Note the typical polar plugs

Endoscopy of the rectum shows the adult worms being attached there at the mucosa.

6. **Pathway of infection**: Oral uptake of contaminated, non-washed or undercooked plants. Due to the lack of a development of immunity, repeated infections are possible as well as self-infections.
7. **Prophylaxis**: Intense washing of agricultural products before eating, avoiding contact with human feces.
8. **Incubation period**: 2–3 months.
9. **Prepatent period**: 3 months.
10. **Patency**: 15–18 months.
11. **Therapy**: Drugs of the choice are mebendazole (2 × 100 mg daily) and albendazole (1 × 400 mg daily). Children below 2 years should be treated by 15 mg/kg bodyweight) always for 3 days.

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4.4.4 *Ancylostoma* and *Necator* Species (Hookworm Disease, Ancylostomiasis, Necatoriasis)

1. **Name**: Greek: *ankylos* = bended, hook-like; *stoma* = mouth. Latin: *duodenalis* = belonging to the duodenum; *necator* = killer; *americanus* = American. English: Old and New world hookworms.
2. **Geographic distribution/epidemiology**: Both species occur in warm and humid regions between 30° south and 45° north, but also worldwide in deep mines. *A. duodenale* is found in North Africa, North and South Asia, while *N. americanus* occurs in America, Central Africa and regions in South and Eastern Asia. Worldwide about 800 million people are infected.
3. **Biology, morphology**: The whitish adults of both species measure about 10–12 mm in length and the species can be clearly differentiated according to the criteria listed in Table 4.7 and by morphological aspects shown in Figs. 4.39

Table 4.7 Characteristics of adult worms of *Ancylostoma duodenale* and *Necator americanus*

Characteristics	*A. duodenale*	*N. americanus*
Mouth	Four visible teeth on two plates	Two half moon shaped cutting plates
Posterior pole of females	With a defined spine and a mucron	No mucron
Position of the female genital opening	Behind the mid of the body	Before the mid of the body
Spicules of male copulatory bursa	Two, diverging from each other and pointed tips	Two, lying close besides each other, ending in barbed hooks
Mean number of excreted eggs per day	~9000 per day	10,000–15,000 per day

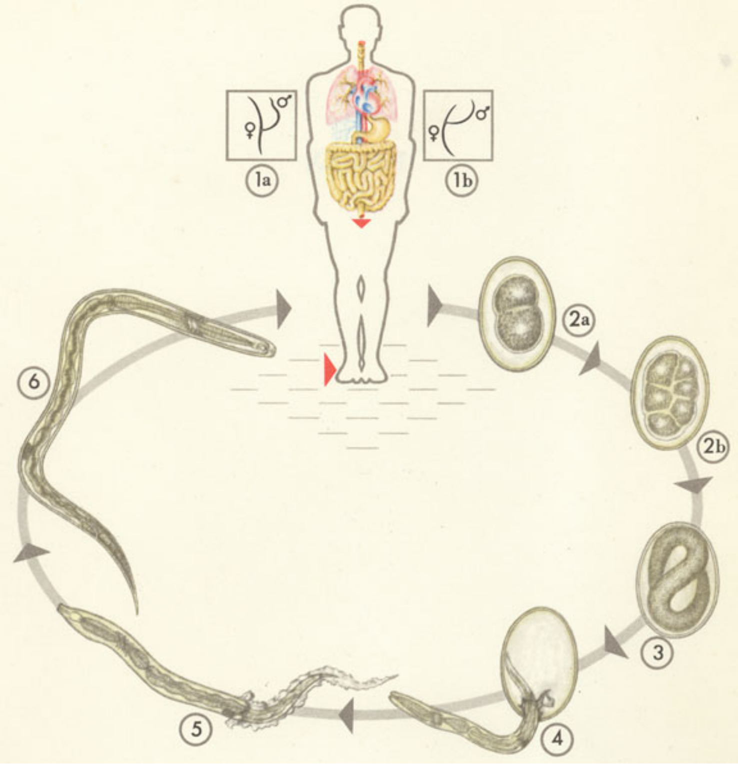

Fig. 4.39 Diagrammatic representation of the life cycles of *Ancylostoma duodenale* and *Necator americanus* (according to Piekarski 1962). (**1a**) Copulation of *A. duodenale*. (**1b**) Copulation of *N. americanus*. (**2a**) Freshly excreted egg. (**2b**) Egg in the 6-cell stage. (**3**) Egg containing larva 1. (**4**) Free rhabditiform larva 1. (**5**) First moult. (**6**) Filariform larva 2, which remains as larva 3 (=penetration larva) after molt inside the sheath

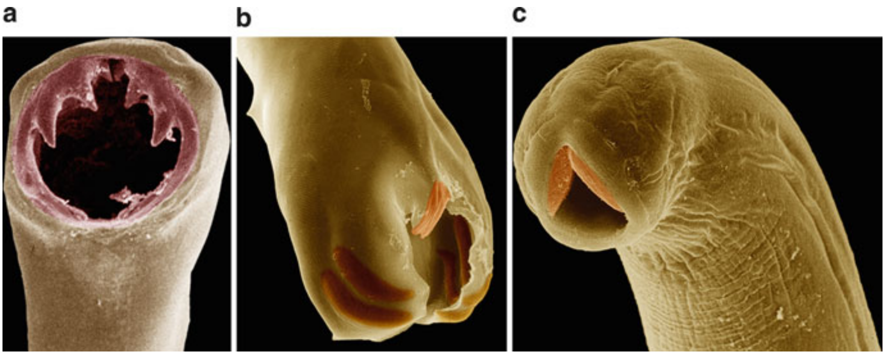

Fig. 4.40 Scanning micrographs. (**a**) Anterior end of *E. duodenale* showing the mouth showing two plates each being equipped with two teeth. (**b**) Posterior end of a male worm of *A. duodenale* showing the so-called bursa copulatrix. (**c**) Anterior end of *N. americanus* showing the two cutting plates inside the mouth

and 4.40. However, the eggs are practically indistinguishable in both species. Males of both species are only slightly smaller than the females; however, they possess a hold-fast organ at their terminal end, which is described as bursa copulatrix, looks hand-like and makes it possible that the males are able to copulate with the females. During copulation which apparently occurs permanently during blood sucking at the intestinal wall, the hand-like bursa copulatrix is firmly attached around the genital opening of the female (Fig. 4.39: 1a, 1b). Since the genital openings of the females of *A. duodenale* and *N. americanus* are not situated at the same region, different copulation pictures occur (Fig. 4.39: 1a, 1b). The worms suck blood mainly in the region of the jejunum. This blood is not only used as food but also helps to supply the worm with oxygen. Therefore, the worms suck much more blood than it is needed for feeding. This behaviour leads to the fact that infected persons discharge blood in their feces and suffer finally from anaemia if large numbers of worms are present. The females excrete per day 9000–10,000 eggs (*Necator americanus* even up to 15,000), which are thin-walled and reach a size of 60×40 μm. In fresh feces, the eggs contain only 2–8 cells. However, under good conditions (warm and humid) the rhabditiform first larva develops within 2 days. Therefore, only fresh feces should be investigated for diagnosis in order to avoid infection of the personnel of the laboratories. Furthermore, this early investigation excludes misinterpretations since the eggs of other nematodes such as *Trichostrongylus* or *Ternidens* sp. look rather similar. After hatching of the larva 1 from the egg outside of the body, two more larvae are formed within 5–7 days. The third one (filariform stage) has a length of 500–650 μm and is still enclosed in the cuticle sheath of the second-stage larva and thus is called a "sheathed" larva.

The **infection of humans** occurs by active penetration of the larva 3 into the skin, whereby the sheath is stripped off. After a heart–lung–trachea–

oesophagus passage (under occasional drifting in other organs), the larvae 3 reach the intestine within 3–7 days, where they become mature within 4–6 weeks. Besides these two common species, humans (but also cats and dogs) may become infected by *Ancylostoma ceylanicum*, which occurs in Taiwan, South-East Asia and Suriname. This species has a similar life cycle like *A. duodenale* and *N. americanus* (Fig. 4.40c) and possesses like *Necator* two cutting plates in the mouth, while *A. duodenale* has two plates with each two hooks (Fig. 4.40a). Further hookworms of animals are *A. braziliense* (America, Asia in dogs, cats, wolves, bears), *A. caninum* (worldwide in dogs, wolves, foxes, tigers, cats, pigs) and *A. tubaeforme* (Europe, in wild and domestic cats). The larvae of these species, however, may also enter the skin of humans, but do not reach maturity, so that they stick somewhere in the organs of the final host. If these larvae (like those of *A. braziliense*) remain in the skin, they may induce skin elevation described as "**larva migrans**" or "**creeping eruption**".

4. **Symptoms of the disease (Ancylostomiasis; hookworm disease)**: About 20–25 % of the human population on earth are (at least occasionally) infected by hook worms. Even in temperate regions, these worms occurred in mines, since down there the temperatures are increased. Thus, names of diseases such as "tunnel disease" and "miner's disease" refer to those infections. In general, the hookworm disease is always connected with considerable blood loss. However, an infection with 30 adults of the species *Necator americanus*, which each suck about 0.03 ml blood per day, may remain unnoted, while 100–500 worms introduce medium sized damages and more than 1000 are life-threatening. *Ancylostoma* worms suck about 10 times more blood than those of *N. americanus*. Thus, in the case of *A. duodenale* already 100 worms lead to severe anaemia. Furthermore, all worms change several times per day their sucking place, while the wounds are still bleeding. This behaviour leads to further considerable blood losses.

   In general, the following phases during an infection with hook worms may be noted:

   - **Skin penetration phase**:
     Itching and formation of papulae at the penetration sites of the larva 3.
   - **Lung passage**:
     Symptoms like bronchitis, lymph node swellings and lung and trachea inflammations.
   - **Acute disease**:
     In cases of mass infections haemoglobin becomes massively decreased, reddish and even black stools are excreted, fever, high-grade eosinophilia.
   - **Chronic phase of disease**:
     This phase is very dangerous, since worms live up to 20 years. Thus, there is a constant blood loss which leads to a considerable weakness of the patient. Further symptoms are abdominal pain, slight fever, obstipation, slightly occult bloody stool, increasing anaemia with consequences such as cachexia, heart and circulation problems, which may lead finally to death. At least 100,000 people die worldwide per year due to heavy infections with

these hookworms—especially young children are severely hit, since they are often double infected with other parasites (protozoans, worms) or with viruses and bacteria.

5. **Diagnosis**: Microscopical demonstration of eggs inside the feces by the help of concentration methods such as sedimentation, M.I.F. or S.A.F. Fresh excreted eggs of the hookworms can be distinguished from eggs of the worms belonging to the genera *Trichostrongylus* and *Ternidens* (e.g. *T. deminutus*) by the fact that they only contain 2–8 embryonic cells, while the eggs of the 2 other genera contain at least 32, 64 or even more cells.
6. **Pathway of infection**: Percutaneous by skin penetration of the larvae 3, which stay alive for weeks in nature. Due to the lack of immune reactions of infected hosts, they can become repeatedly infected, thus enlarging their parasitic load for a long phase of their life.
7. **Prophylaxis**: Wearing of firm shoes in endemic regions, avoidance of contact to human feces. **Attention**: Working in laboratory with hookworm eggs must consider the fact that larvae hatch very quick; thus, tables and vessels must be intensively cleaned.
8. **Incubation period**: A few hours after penetration of the larva 3 signs of dermatitis occur, while about 2 weeks after the percutaneous infection the intestinal symptoms start to increase.
9. **Prepatent period**: 5–6 weeks.
10. **Patency**: Up to 20 years.
11. **Therapy**: Drugs of choice are mebendazole (2 × 100 mg for 3 days) and albendazole (1 × 400 mg; children below 2 years 15 mg/kg bodyweight). Also further anthelmintics are effective: e.g. ivermectin, levamisole, pyrantel or bephenium. In cases of anaemia, iron substitution is obligatory; in extreme infections even blood transfusions may be needed.

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4.4.5 *Strongyloides stercoralis*

1. **Name**: Greek: *strongylus* = rounded; *oides* = similar. Latin: *sterx* = posterior end; *stercus* = feces; *stercoralis* = inside feces. English: Dwarf threadworm.
2. **Geographic distribution/epidemiology**: This worm species is found in humid-warm regions of subtropical and tropical regions, but also in South Europe. Many thousands of humans are infected. In former times, it also occurred in European mines. **Attention**: Also monkeys in zoological gardens are worldwide infected. However, its free-living stages need an average temperature of at least 15 °C for further development.
3. **Biology, morphology**: *S. stercoralis* forms two generations within its life cycle (Figs. 4.41, 4.42 and 4.43). There exists a parasitic generation of females inside the host's intestine (Fig. 4.41A). The 2.0–2.5 μm × 50 μm sized females produce eggs parthenogenetically (=without males). In these eggs, rhabditiform larvae develop and emerge from the eggs while the eggs are still in the lumen of the intestine. For this reason, they are easily found in the freshly passed feces of man, especially as they are actively motile. Outside the host they become the infective, so-called filariform larvae (about 500 μm in length) which can actively penetrate the intact skin ("**direct development**", **A**).

   The rhabditiform larvae can, under conditions not precisely known, develop into filariform stages even in the intestine of the same person. They are able to penetrate into the intestinal wall (leading to a so-called **endo-autoinfection**, **C**), or they penetrate into the skin outside of the intestine (the so-called **exo-autoinfection**).

   In addition to this direct development (Fig. 4.41A), an alternation of generations can also occur (Fig. 4.41B). In these cases, rhabditiform larvae give rise, outside the host, first to a bisexual generation. The females of which then lay fertilized eggs. In these eggs, rhabditiform larvae are formed and these can become either filariform larvae or free-living, unisexual worms ("**indirect development**", Fig. 4.41B). After penetration of the skin, the 500–700 μm long filariform larva starts a migration phase inside the host. It travels via the venous system to the right heart chamber and from there to the lungs, where the larvae leave the blood vessels and thus reach the alveoli. From there they migrate up to the bronchioles, bronchi and trachea to the epiglottis, then they are swallowed and thus reach via the stomach the mucosa of the small intestine, where they become parthenogenetic females (Fig. 4.43c). At least 17 days are

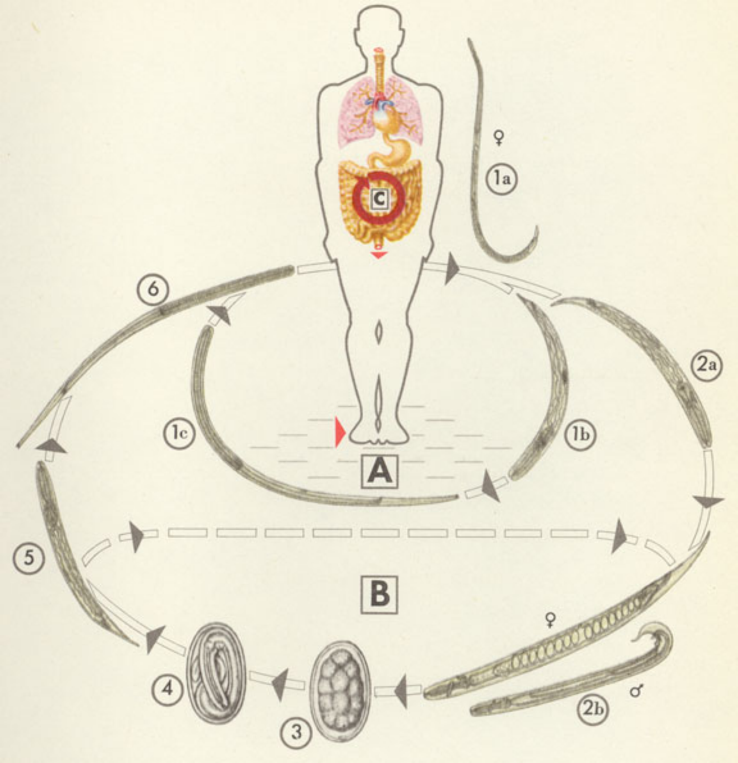

Fig. 4.41 Diagrammatic representation of the life cycle of *Strongyloides stercoralis* according to Piekarski (1962). (**A**) Infection; (**B**) Development outside of the human body; (**C**) Development inside the intestine (e.g. autoinfections). (**1a**) Parthenogenetic female inside the intestine; (**1b**) Larva 1 (rhabditiform) in fresh feces; (**1 c**) Filariform larva 3 = infectious stage; (**2a**) Larva 1 (rhabditiform) in fresh stool; (**2b**) Male and female adults; (**3, 4**) Development of the larva in the eggs of the sexual generation; (**5**, **6**) Rhabditiform (**5**) and infectious filariform (**6**) larvae

required between the entry into the host (by penetration of the skin) and the appearance of larvae in the feces (prepatent period!).

4. **Symptoms of the disease (Strongyloidiasis)**: During the migration of the larvae through the lung, symptoms like those of bronchitis or bronchopneumonia may occur. Migrating larvae, which pass through regions of the skin, may induce the aspect of a so-called "creeping eruption"—motile skin elevations. After the entrance of the parasite into the intestine (after a successful heart–lung–throat–oesophagus passage), abdominal symptoms of disease occur, which may vary due to the amount of parasitic stages. Very often the following symptoms have been described: long-lasting slimy to fluid diarrhoeas which sometimes contain blood. These diarrhoeas may be interrupted by phases of obstipation. All this may be accompanied by a general weakness and loss of bodyweight. The blood picture shows a strong eosinophilia, leucocytosis and

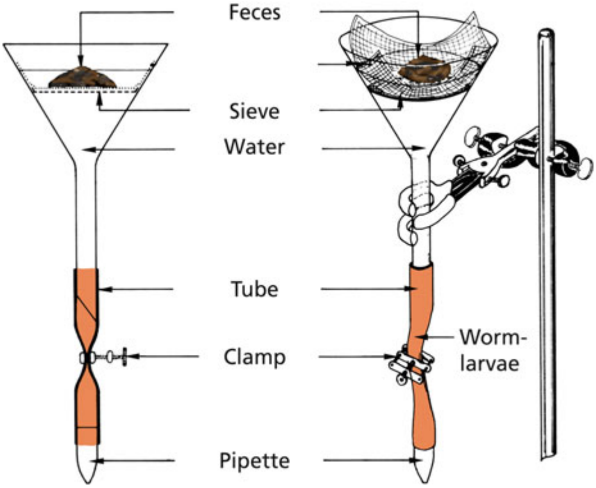

Fig. 4.42 Baermann's larval concentration method. Diagrammatical representation of two aspects of the Baermann funnel, which is used to concentrate larvae of nematodes that occur in human stool. The larvae are finally present in the fluid below the clamp

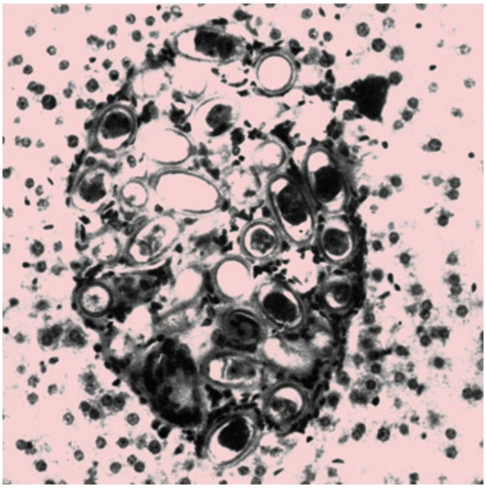

Fig. 4.43 Section through a piece of liver containing a "nest" of *Capillaria hepatica* eggs. They show the typical polar plugs, which are typical for *Trichuris* species

anaemia. In cases of mass infections and immune suppression (e.g. in cases of AIDS patients), death may be the consequence.

5. **Diagnosis**: The most effective method is to examine microscopically the feces or the duodenal fluid for the occurrence of motile larvae. However, in cases of low-grade infections the use of an enrichment method is recommended (such as the Baerman method) (see Table 4.8). Immunodiagnostic methods such as ELISA or Western Blot are very sensitive; however, their specifity is low, so that there may occur cross reactions with stages of filariae or hookworms.

A further *Strongyloides* species is named to honour the German scientist Fülleborn (*S. fuelleborni*). This species is described to occur mainly in monkeys, but was also found in humans.

Table 4.8 Species of the genus *Trichinella*

Species	*Hosts*	*Distribution*
T. britovi	Fox, wolf, bear, pig, horse, **humans**	Eurasia, Africa, Europe
T. murrelli	Fox, racoon, bear, horse, dog, cat, **humans**	North America
T. nativa	Bear, wolf, fox, wildcat, tiger, boar, dog, cat, **humans**	Arctic and Subarctic, North America, Eurasia, Europe
T. nelsoni	Lion, leopard, wild African animals, **humans**	Africa, South of the Sahara
T. papuae	Boar, pig, **humans**	Papua Guinea, Thailand
T. pseudospiralis	Racoon, badger, boar, pig, cat, cat, birds, marsupialia, **humans**	Worldwide
T. spiralis	Pig, boar, horse, cat, dog, fox, bear, rat, **humans**	Worldwide
T. zimbabwensis	Crocodile, Nile-varan	Ethiopia, Zimbabwe, Mozambique, South Africa

6. **Pathway of infection**: Percutaneously by penetration of larvae 3 (=filariform stage) into the skin of humans in endemic regions. If tourists are infected there they may become further auto-infected by larvae, which develop themselves inside the intestine and become further anchored at the mucosal layer of the intestine.
7. **Prophylaxis**: Use of stabile shoes in endemic regions and avoidance of contacts to human feces or that of monkeys. **Attention**: In laboratories: The use of gloves is obligatory; in hospitals: **Caution**: avoid contact to feces of immunocompromised persons.
8. **Incubation period**: 12–18 h in the case of skin reactions, 1 week to see lung reactions and 2 weeks are needed for the occurrence of intestinal symptoms.
9. **Prepatent period**: 14–21 days after percutaneous penetration of the larvae.
10. **Patency**: Up to 40 years after repeated autoinfections (noted in soldiers after the Second World War).
11. **Therapy**: The drug of choice is albendazole (400 mg daily for 3 days). Tiabendazole (2 × 25 mg/kg bodyweight for 3 days) is also highly effective and has, however, some adverse side effects. Furthermore, mebendazole (2 × 200 mg daily for 7 days) has been shown to control such an infection, too. Due to the high rates of autoinfections, the therapy should be repeated after 3 weeks. Several controls of the feces and blood status should be done for a longer period. In cases of a so-called hyperinfection syndrome, it is recommended to use albendazole for 5–7 days (2 × 400 mg daily; for persons below 60 kg: 15 mg/kg bodyweight daily in two doses daily). Alternatives are again tiabendazole and mebendazole. There are also publications, which show that ivermectin is effective, too. In cases of therapy resistance albendazole (doses see above) or mebendazole (60 mg/kg bodyweight daily, divided in three doses) has to be ingested daily for 4 weeks.

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Luviro V et al (2014) Management of *Strongyloides stercoralis*: a puzzling parasite. Int Health 6:273–281

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4.4.6 *Capillaria* Species (Capillariasis)

4.4.6.1 *Capillaria hepatica*

1. **Name**: Latin: *capillaris* = belonging to hair, hair-like; *hepaticus* = belonging to liver; the name refers to the hair-like shape of the adult worms. English: Capillary worm. The genus name *Calodium* is a synonym.
2. **Geographic distribution/epidemiology**: Worldwide, several hundred thousand humans are infected.
3. **Biology, morphology**: The adult worms which belong to the family of Trichuridae in the group of nematodes parasitize in the liver parenchyma mainly of rodents but also of humans, rarely in horses, dogs, cats and pigs. The females reach a length of 5.8–10 cm × 0.2 mm and as males they measure 2.5–3.7 cm × 0.5 mm. The females depone their eggs (45–60 μm × 30–35 μm) inside the liver parenchyma, from where they are only released if carnivores ingest infected liver tissues. Thus, a transmission from humans to humans is in general not possible. The eggs excreted by carnivores develop outside of a body the infectious larva. The **infection of humans** and specific final hosts thus occurs when eating or feeding salad or other plants which are contaminated with fecal remnants of such carnivores.
4. **Symptoms of the disease**: In humans: unspecific symptoms, which have their origin in tissue destruction due to adult worms in the liver (Fig. 4.43c). Thus, *Capillaria hepatica* infections of humans are very often only detected in cases of post-mortem examinations. Most clinical symptoms are unspecific.
5. **Diagnosis**: Microscopy of histological sections of liver and rather unspecific serological indications show the presence of nematodes inside the body. PCR techniques offer better information.
6. **Pathway of infection**: Oral uptake of infectious eggs excreted by carnivores that had ingested infected livers of, e.g., rodents.
7. **Prophylaxis**: Washing of salad and raw vegetables.
8. **Incubation period**: Unknown.
9. **Prepatent period**: Eggs are not excreted by humans.
10. **Patency**: In humans: lifelong, although adult worms live only 1–2 years, but eggs will stick very long in liver tissues.
11. **Therapy**: Unknown; nematocides like albendazole or ivermectin will kill the adults and thus stop egg production.

Further Reading

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Gomes EJ et al (2015) Study of the prevalence of *Capillaria hepatica* in humans and rodents in an urban area of the city of Porto Velhi, Brazil. Rev Inst Med Trop Sao Paulo 57:39–46

4.4.6.2 *Capillaria philippinensis* (Capillariasis)

1. **Name**: Greek: *capillaris* = hair-like; the species name refers to the country where this species was first described in the year 1963.
2. **Geographic distribution/epidemiology**: On the Philippines and several Pacific islands, several hundred thousands humans are infected.
3. **Biology, morphology**: These worms (females 2–5 mm long, males 2 mm, with diameters of 50–100 μm) live attached at the mucosa of the intestine of humans and some animals. The eggs look like those of *Trichuris* sp. and measure about 45 × 20 μm in size. The eggshell is rather thick, appears striated and their two polar plugs are not protruding. The females excrete unembryonated eggs, which develop within 10–14 days the first-stage larva. If such eggs drop into water, they may be ingested by specimens of several fish species. Inside the intestine of these intermediate hosts, the larva hatches from the egg, enters the intestinal wall and reaches via the bloodstream the muscles. After about 3 weeks, the adult stage is developed. If humans or other fish-feeding mammals ingest such larvae-containing muscles of fish, they become infected and the adults will be formed inside the intestine within about 3 weeks. It is not yet clear whether the *Capillaria* species of birds may be also infectious to humans.
4. **Symptoms of the disease (Capillariasis)**: The gravity of the disease induced by *C. philippinensis* adult worms inside humans depends on the total worm load. Large amounts of worms lead to strong, watery diarrhoeas (up to 8 times per day), which may introduce secondary symptoms such as function loss of organs. Severe infections may be life-threatening.
5. **Diagnosis**: Microscopically demonstration of the typical eggs inside the feces. In the case of diarrhoeic stools, also adult worms may become discharged.
6. **Pathway of infection**: Oral by eating raw or undercooked larvae 3 containing meat of fish.
7. **Prophylaxis**: Cooking or grilling fish meat before consumption.
8. **Incubation period**: Exact data are unknown.
9. **Prepatent period**: Exact data are unknown.
10. **Patency**: Unknown
11. **Therapy**: Albendazole (1–2 × 400 mg daily) or mebendazole (2 × 200 mg daily) has to be ingested for 3 weeks. Due to formation of recidives, sometimes several months of permanent treatment are needed.

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Scullion F (2013) A simple method to count total faecal *Capillaria* worm eggs in racing pigeons (*Columba livia*). Vet Parasitol 197:197–203

Tamaru M et al (2015) Morphological and moleculargenetic characterization of three *Capillaria* species (*C. anatis*, *C. pudendotecta,* and *C. madseni*) and *Baluscapillaria obsignata* (Nematoda: Trichuridae: Capillariinae) in avians

4.4.7 *Trichinella spiralis* and Related Species (Trichinellosis)

1. **Name**: Greek: *trichos* = tiny hair; *spira* = spiral. Latin: *spiralis* = rolling in. English: Trichinal muscle worm.
2. **Geographic distribution/epidemiology**: Worldwide at least 40 million humans are infected by one of the eight *Trichinella* species and/or a related genotype (Table 4.8).
3. **Biology, morphology**: *Trichinella* worms are known since long (1835) when Richard Owen and James Paget first described this nematode at the British Museum in London, GB (Campbell 1983). The principal life cycle was described by the famous German pathologist Rudolph Virchow (1821–1902) in Berlin, Germany. At first it was thought that there exists only one single species, but today molecular studies showed that at least eight species exist, of which seven may also infect humans (Table 4.8).

   In this chapter, most details described originate from *T. spiralis*. The adult worms measure as females 3–4 mm × 60 μm and as males 1–1.6 mm × 50 μm (Figs. 4.44, 4.45 and 4.46). The adults live only for some (4–6) weeks in the intestine of carnivores or omnivores (e.g. humans, monkeys, pigs, bears, etc., but are recently also found in horses after ingestion of carrion-feeding beetles (Figs. 4.44, 4.45, 4.46 and 4.47). The females produce about 2000 larvae, which measure 90–120 μm in length, enter within 1–2 days the intestinal wall and are drifted by the bloodstream into muscles, where they enter cells (Figs. 4.44 and 4.47). They are also found in cells of other organs. The penetrated larvae lie directly among the muscle filaments (and are not enclosed in a parasitophorous vacuole). Heart muscle cells as well as the polynuclear muscle fibres may become infected, too. After short the parasites induce intensive changes in the interior of the host cell: the nuclei hypertrophy reaching a ten times larger size and the typical inner filamentous arrangement of the muscle cells is replaced by dedifferentiated plasmatic contents (Fig. 4.47a). The infection of humans occurs during oral uptake of such muscle larvae inside raw or undercooked meat, which originates mostly from pigs, bears or seals. In the intestine of humans and carnivores, the muscle fibres are digested and the larvae are set free and grow up within 5–7 days to sexually differentiated males and females. The latter become anchored by the help of

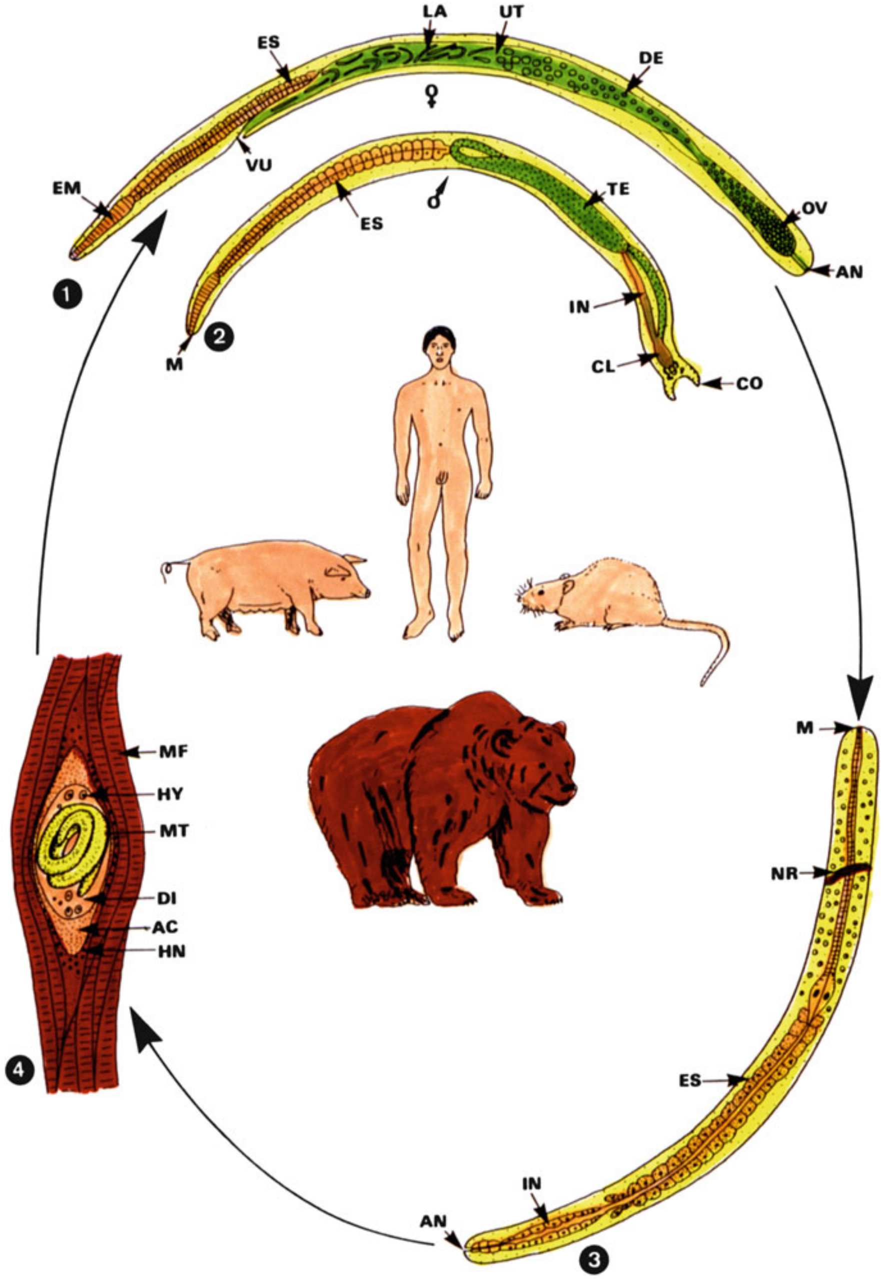
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Fig. 4.44 Diagrammatic representation of the life cycle of *Trichinella spiralis*. (**1**) Female; (**2**) Male; (**3**) Larva 1 inside the intestine; (**4**) Larval stage = muscle larva inside muscle cell. *AC* anlage of a capsule, *AN* anus, *CL* cloaca, *CO* copulatory appendices, *DE* eggs (during larva development), *DI* altered cytoplasm, *EM* muscular region of the oesophagus, *ES* strichosomal portion of the oesophagus, *HN* host cell nucleus, *HY* hypertrophied muscle cell, *IN* intestine, *LA*

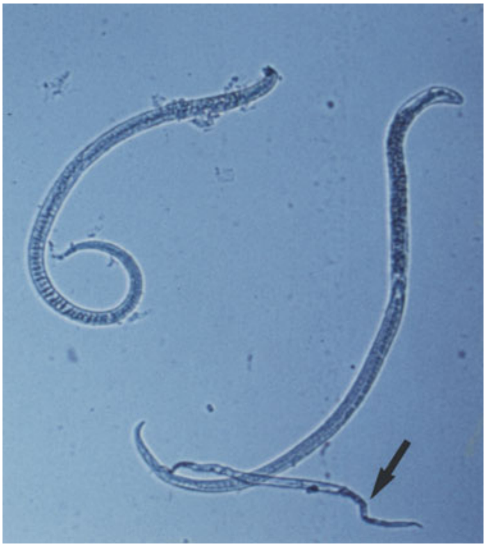

Fig. 4.45 Light micrograph of two females (=large worms) and one small male (*arrow*) of *T. spiralis*

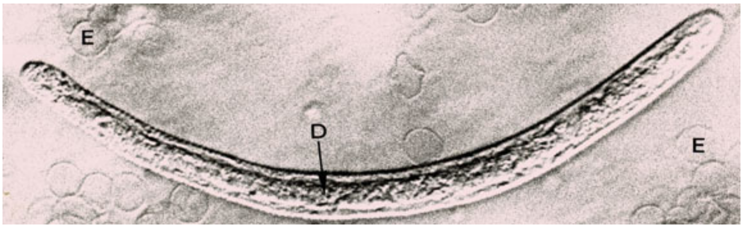

Fig. 4.46 Light micrograph of a just hatched larva 1 inside the blood stream

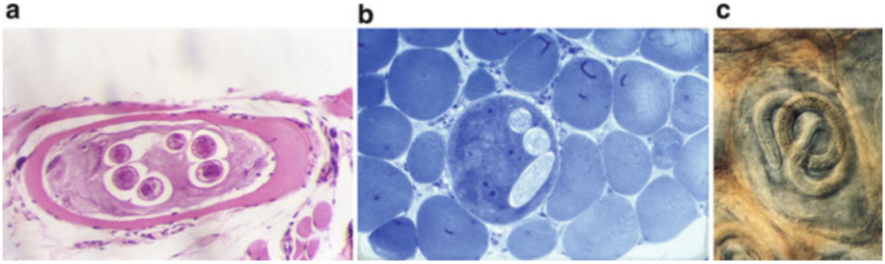

Fig. 4.47 Light micrographs of sections through muscle fibres containing larvae of *T. spiralis*. (**a**) Paraffin section. (**b**) Semithin section. (**c**) Squeezed preparation. The larvae are cut several times. In (**a**) the interior of the host cell is already intensively dedifferentiated

Fig. 4.44 (continued) larval stage, *M* mouth, *MF* muscle fibre, *MT* muscle trichine (=larva 3), *NR* neural ring, *ON* ovary containing eggs, *TE* testes, *UT* uterus, *VU* vulva their anterior end at the intestinal mucosa and give birth (after copulation) for 4–6 weeks of several hundreds of 100 μm long larvae 1 (Fig. 4.44).

4. **Symptoms of the disease (Trichinosis, trichiniasis)**: After an incubation period of 5–7 days, first symptoms occur, the intensity of which depends on the amount of ingested larvae. While a low number of ingested larvae may be completely hidden, large numbers may induce severe symptoms sometimes leading to death. Heavy infections lead initially to abdominal pain, vomiting and diarrhoeas. Starting with the phase when larvae enter the muscle cells/fibres (about 6th–11th day p.i.), the following symptoms often occur:
   - Oedemas in the face region—often combined with conjunctivitis
   - Fever for days up to weeks
   - Muscle pain and in the case of involvement of the breast muscles breathing problems may occur
   - Pneumonia
   - Blood eosinophilia (up to 90 %)

     Severely diseased persons recover very slowly (often only after several months). Death may occur in untreated cases due to myocarditis, acute pneumonia, collapse of circulation or (rather seldom) by embolic events and encephalitis.
5. **Diagnosis**: *Trichinella* infections are mostly detected by the occurrence of the above-listed symptoms but also a high-grade eosinophilia and an enormous increase of the kreatinine kinase inside the serum are very distinctive indications for such an infection. The larvae are best shown in digested material of muscle biopsies after trypsin digestion. Only at the start of an infection, dead adults might be seen in fecal probes. Antibodies can be shown at an early stage of the infection by tests like ELISA, IFT, etc. However, cross reactions with filariae, other nematodes or even schistosomes are possible. Very sensitive are the indirect immunofluorescence method (IIFT), the indirect haemagglutination test (IHA) or different PCR systems.
6. **Pathway of infection**: Oral by uptake of raw or undercooked meat of infected animals (mostly pig meat, especially wild boars are heavily infected). In the last year, also a number of cases were described that human infections occurred after eating undercooked horse meat. The horses apparently had been infected on the meadow while feeding grass containing beetles which had ingested *Trichinella*-infected carrion.
7. **Prophylaxis**: Especially in countries without intense meat control, pig meat should be eaten only well done or after it had been stored at −18 °C for at least 2–3 weeks. Meat of wild boars and meat of bears should be eaten only well done.
8. **Incubation period**: 1–28 days depending on the amount of ingested larvae and also depending on the virulence of the ingested *Trichinella* species (see Table 4.8).

9. **Prepatent period**: Starting on the 5th–6th day p.i., the females release infectious larvae, which can be diagnosed within the blood and already seen inside muscle cells.
10. **Patency**: Up to 20 years.
11. **Therapy**: treatment should start as early as possible. Albendazole (2 × 400 mg per day; children 15 mg/kg bodyweight) for 14 days or mebendazole (3 × 20 mg/kg bodyweight daily) and tiabendazole (2 × 25 mg/kg bodyweight daily) are as well very effective if given for 14 days. In cases of severe symptoms due to huge numbers of parasites, it is recommended to use in corticosteroids in high dosages.

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Pozio EW (2011) Trichinellosis. In: Palmer SR et al (eds) Textbook of zoonoses, 2nd edn. Oxford University Press, Oxford, pp 755–766

Sofronic-Milosavljevic L et al (2015) Secretory products of *Trichinella spiralis* muscle larvae and immune modulation. J Immunol Res, Article ID 523875

4.4.8 *Angiostrongylus cantonensis* (Angiostrongyliasis)

1. **Name**: Greek: *angeion* = vessel; *strongylus* = round, rounded. Latin: *cantonensis* = belonging to the town Canton (today Guangzhou), which is the capital of a region in South China close to Hongkong. English: Pulmonary artery worm.
2. **Geographic distribution/epidemiology**: East Asia, pacific region between 23° N and 23° S (inclusively Hawaii), focally in China and in Japan (especially on the island Okinawa). Especially children are infected while playing with snails, which are intermediate hosts. Several hundred thousands of humans are infected.

3. **Biology, morphology**: This nematode (males 16–19 mm, females 21–25 mm) was detected and first described as a parasite of rats, where it is located inside the heart and in the pulmonary artery. During the last 20 years, numerous infections of humans were described, so that in these regions laboratories are well informed on diagnostic and treatment needs. In rats, the larvae hatch in the lung from the eggs, which are laid unembryonated by female worms. The larvae 1 then migrate via trachea into the mouth region and are set fee into the surrounding nature either via saliva or after intestinal passage via feces. Outside of the body, the larvae have to be ingested by an intermediate host wherein they are stored and develop into the infectious larva 3 (Fig. 4.48). It was found that snails of the genera *Biomphalaria* and *Archachatina* become such intermediate hosts as well as land or freshwater crabs. Inside their tissues, the ingested larva 1 develops via larva 2 to the infectious larva 3. The **infection of humans** and that of the specific final hosts (rats) occur by ingestion of raw snail meat (Fig. 4.49). The larva 3 is set free in the human or rat host inside the intestine and migrates into the brain. After a phase of about 4 weeks, the larvae return to the lung and stay in the pulmonary arteries, where they reach maturity and produce eggs which are set fee within sputum or feces. In the case of humans, this typical life cycle is interrupted in the brain, since the larvae 3 or pre-adults remain there (or in the eyes of other organs) and do not migrate to the lung. Thus, they never reach maturity in humans. Due to this fact, these resting worms lead to severe damages inside the parasitized organs.
4. **Symptoms of the disease**: In all cases of a clearly diagnosed infection of humans with *A. cantonensis* worms, the symptoms of an **eosinophilic meningoencephalitis** are shown, which starts with cerebral dysfunction leading to paresis of the fascialis nerve, paraesthesia along the legs and arms and finally to burning pain along the rump after an incubation period of about 3 weeks. When passing the eyes, the migrating larvae may also induce the complete loss of function. On the other hand in about 40 % of human infections, the symptoms remain low grade so that the affected persons must not be treated. In any case, however, the severity of the symptoms always depends on the amount of the wandering larvae.
5. **Diagnosis**: In the case of infected humans, the direct diagnosis by microscopical inspection of the saliva or feces is not successful, since neither eggs nor larvae are excreted. The finding of the about 500 μm long larvae 3, which are ingested when eating infected raw meat of crabs, of snails or of other infected intermediate hosts (Fig. 4.49), is a rare event. Thus, the demonstration of the extreme numbers of eosinophilic granulocytes (e.g. 10–90 % eosinophils) in coloured smear preparation is the most important method. In addition, ELISA tests give good results, while computer tomography shows brain damages.
6. **Pathway of infection**: Oral uptake of L3 larvae within raw or insufficiently cooked muscles of true intermediate hosts (e.g. snails, crabs; in some regions about 10 % of those animals are infected!), but also in meat of so-called transportation hosts (cattle, pigs), which became infected by accidental ingestion of infected snails.

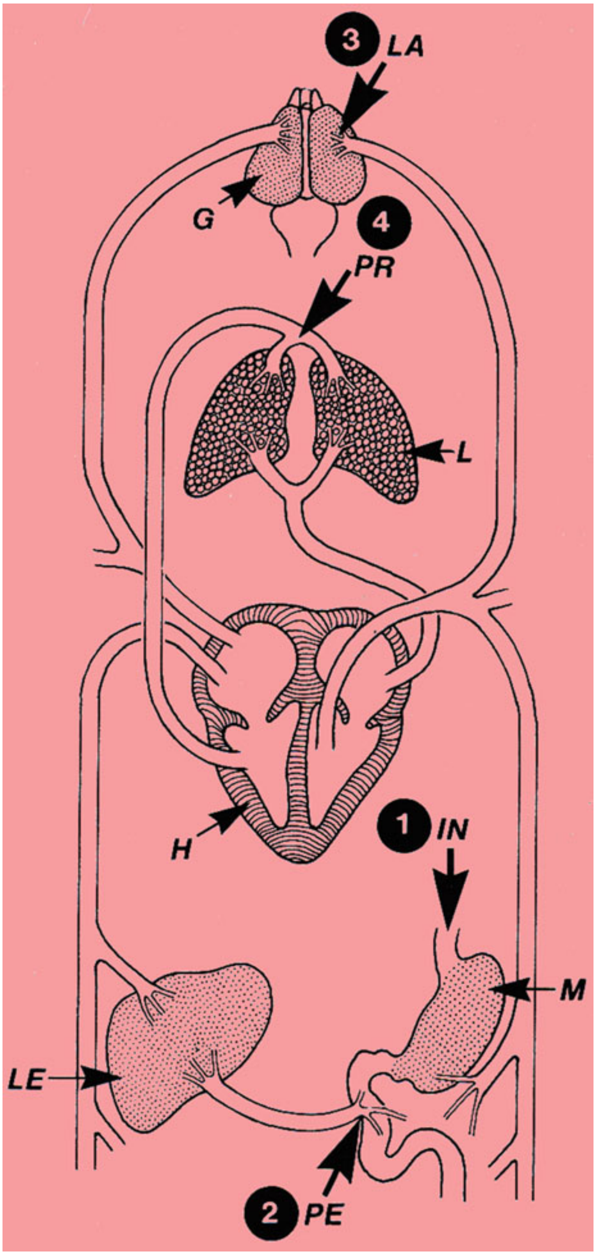

Fig. 4.48 Diagrammatic representation of the pathway of infection and the different habitats of the developmental *Angiostrongylus cantonensis* in rats. In the case of infected humans the larvae remain in the brain and/or eyes. (**1**) **IN** Infection during oral uptake of larval containing intermediate hosts (e.g. snails, crabs). (**2**) **PE** Penetration of the larvae 1 into the intestinal wall and into the mesenterial veins of the intestine. (**3**) **LA** Staying of the larvae 3 in the brain (after a heart–lung passage). (**4**) **PR** Staying of the pre-adults inside the lung arteries. *G* brain, *H* heart, *L* lung, *LE* liver, *M* Stomach

7. **Prophylaxis**: Food in endemic regions should always be eaten well done or intensively washed (e.g. plants). Avoid hand-mouth contacts after handling potentially infected snails.
8. **Incubation period**: 2–3 weeks.

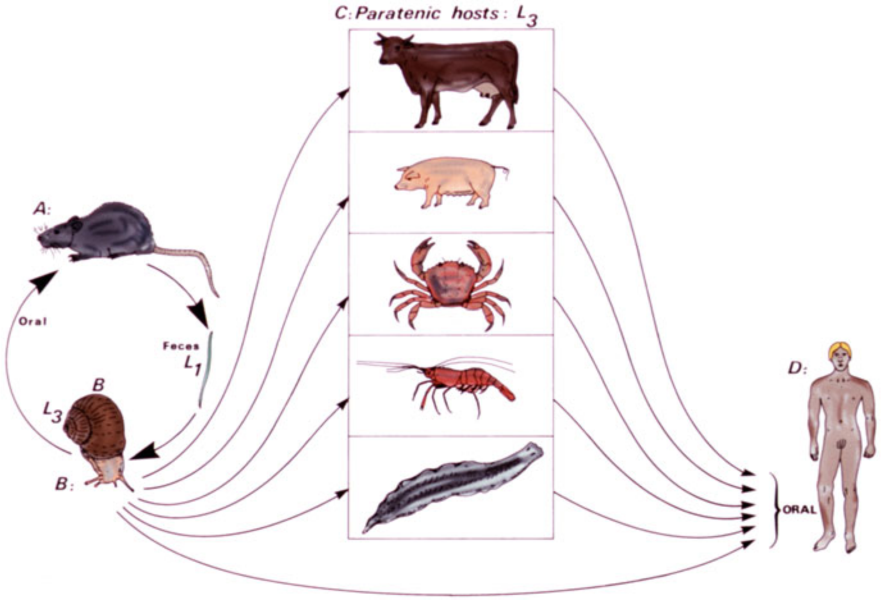

Fig. 4.49 Diagrammatic representation of the life cycle of *Angiostrongylus cantonensis*. (**A**) Final host (final host), (**B**) Intermediate host, (**C**) Paratenic host (they contain larvae), (**D**) Erroneous host. The final hosts (rats) and the paratenic hosts as well as humans may become infected by ingestion of infected snails or larval containing slime

9. **Prepatent period**: Larvae 3 enter within 2–3 days after infection the brain and can be shown in the fluid.
10. **Patency**: it takes months until the migrating larvae die.
11. **Therapy**: Larvae occurring in the eyes should be surgically removed. Mebendazole and tiabendazole were successful, if doses of 25 mg/kg bodyweight are given 1–2 times daily on 2–3 consecutive days. Also albendazole (15–20 mg/kg bodyweight) as well as levamisole and ivermectin showed significant efficacy on migrating larvae. However, the simultaneous killing of numerous larvae may induce considerable allergic reactions. Therefore, it is recommended to apply besides the anthelmintics also antihistamines (c.f. corticosteroids).

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4.4.9 *Angiostrongylus costaricensis (Angiostrongyliasis)*

1. **Name**: Greek: *angeion* = vessel; *strongylus* = round, rounded. The name refers to the site of the worm inside humans and to the country where this worm had been first described (Costa Rica, Central America). English: American mesenterial worm.
2. **Geographic distribution/epidemiology**: Regions in Southern USA, Central America, Venezuela, Colombia and Brazil with reduced hygienic conditions are the main regions. Several thousands of people are infected there.
3. **Biology, morphology**: Main hosts of *A. costaricensis* are rats, where the adult worms live in the mesenterial veins (arteries) of the intestinal tract (with a special concentration on the regions of the ileum and caecum). The adult female worms reach there a length of 33 mm; the males measure only 20 mm. The ovoid eggs (excreted after copulation) are thin walled and measure about 90 µm in their longitudinal diameter. Within the bloodstream, these eggs reach the blood vessels of the mucosa and submucosa, where the formation of the larva 1 occurs inside the egg and (in the case of rats) also the hatching of the about 260 µm long larvae. These larvae enter the lumen of the intestine and are finally excreted within the feces, while in the case of human infections these larvae remain in the blood vessels. These larvae 1 are finally ingested by snails (e.g. genus *Vaginulus*) and are transformed therein within 18 days via larvae 2 to larvae 3. In the case that rats ingest such infected snails, these larvae enter the blood vessels of the intestinal wall and grow up to reach **within 24 days** maturity. Finally, they settle in the mesenterial veins. It was recently shown that also dogs may be final hosts.
4. **Symptoms of the disease**: Since in the case of humans the larvae do not leave the blood vessels of the intestinal wall (ileosacral region) inflammations, thrombosis and necrosis are induced there leading to abdominal pain (acute abdomen). The intestinal wall becomes as strong influenced that partial or total occlusions of the intestine may occur (Ileus verminosus). The blood status shows a high-grade eosinophilia accompanied by a considerable leucocytosis.
5. **Diagnosis**: Since in the case of humans larvae (260–290 µm × 14–15 µm) are found only rarely in the feces, diagnosis has to been done on the basis of microscopical examination of histological sections after surgery. Well-defined serologic test systems are not yet developed.

6. **Pathway of infection**: Orally after contact with slime of infected snails. Thus, mainly children (playing with infected snails) are infected or persons eating raw snails.
7. **Prophylaxis**: Avoidance of contact with such snails.
8. **Incubation period**: About 3 weeks until first occurrence of abdominal symptoms.
9. **Prepatent period**: In the case of rats: about 24 days.
10. **Patency**: About 1–2 years (in rats).
11. **Therapy**: In the case of humans, tiabendazole is the drug of choice (75 mg/kg bodyweight for 3 days). However, mostly additional surgical removal of worms is needed.

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4.4.10 *Anisakis* Species and Related Species (Anisakiasis)

1. **Name**: Greek: *anisos* = different; *akon* = hook. Latin: *simplex* = simple. English: Herring worm, cod worm etc.
2. **Geographic distribution/epidemiology**: Worldwide, especially people living along the coasts of Asia, Canadian and European shore. Many hundred thousands of persons become infected (mostly undiagnosed) from time to time.
3. **Biology, morphology**: In the case of the three here selected species (a–c), the adult worms belong to the so-called roundworms (like *Ascaris*), which live as adults in marine predators such as dolphins, seals, whales, etc., which thus are the final hosts. These worms do not reach the adult stage in humans, when they have eaten the second-stage larvae of these species, which are rather common in many fish species. Inside humans, these larvae migrate inside the tissues after leaving the intestine (Figs. 4.50 and 4.51).

   The following important three species have been described in the literature in more detail than others:

   (a) *Pseudoterranova decipiens* (syn. *Phocanema* sp., *Terranova* sp.)

      The adult worms use seals as final hosts, where they parasitize inside the intestine reaching a length of up to 20 cm and excrete eggs which develop outside of the body the larva 1 inside and become finally ingested by small crustaceans in the water biotope. Inside these small crustaceans

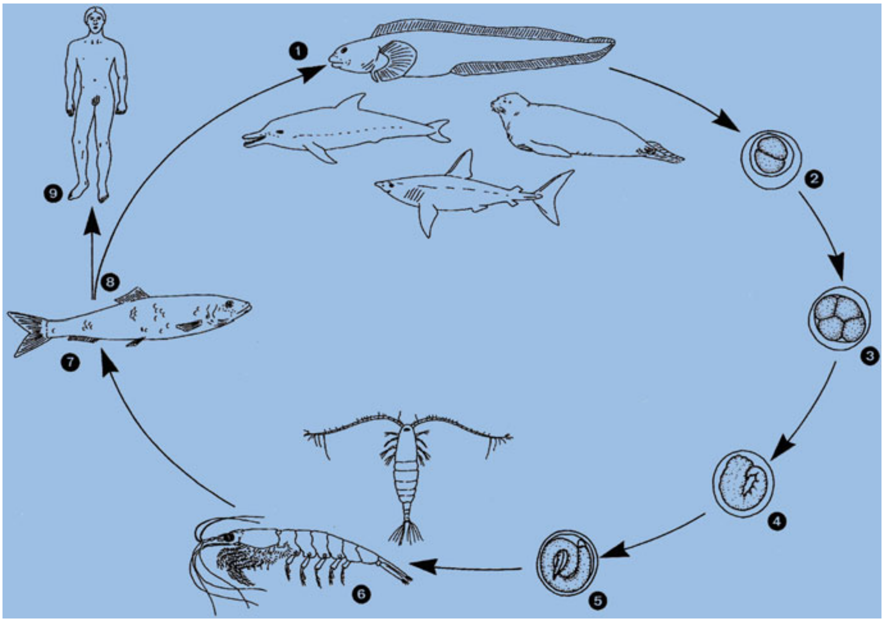


Fig. 4.50 Diagrammatic representation of the life cycle of *Anisakis* species and related species. (**1**) Typical final hosts. (**2–5**) Larval development inside eggs in open water. (**6**) Small crustaceans as first intermediate hosts, which ingest such eggs. (**7**, **8**) Fish as second intermediate hosts: the included larvae develop into adults worms, if they are ingested by final hosts (**1**). (**9**). Humans as accidental host; however, larvae do not become mature in humans

(intermediate host 1), the larva 1 is transformed to larva 2, which develops inside fish (as intermediate host) into the larva 2. When the second intermediate host fish ingests such larvae 2 containing small crustaceans the larva 2 develops inside his muscles or intestine into larva 3, which is infectious for the final hosts, where the adult worm is developed. However, if humans eat such larvae-bearing fish at a raw or undercooked stage, the worms do not reach maturity but enter the wall of the stomach and/or intestine and lead often to considerable damages.

(b) *Anisakis simplex* (syn. *Acanthocheilus* sp., *Eustoma* sp.)

The whitish, about 30 mm long larvae are common in herrings (therefore this species is called herring worm) but always found in more than 20 other fish species and even in cephalopods. They are characterized by an intestine without any diverticles (Fig. 4.51a), by the possessing of a boring tooth at the anterior pole and a slight pike at the hind end. The infection rates in herrings reach 58 % and up to 78 % in other fish, where up to 7 worms were found within 1 kg fish meat, so that raw eating would lead to a high ratio of infections. **Final hosts** of *A. simplex* are different species of whales and apparently also some species of seals. The females of these worms reach a length of 30 cm; the males measure only 16 cm.

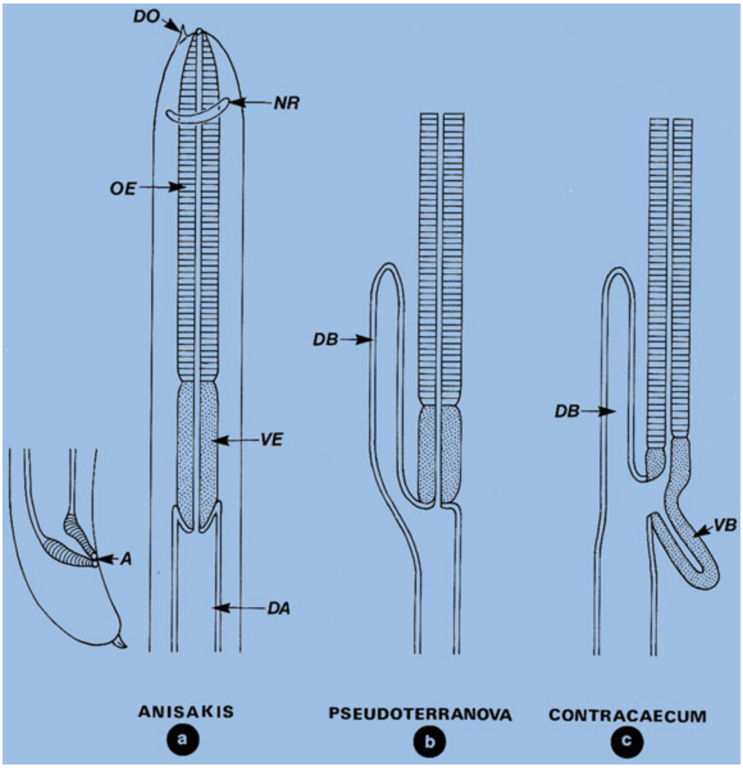


Fig. 4.51 Diagrammatic representation of the anterior ends of the third-stage larvae of important human pathogenic anisakids. *Left*: terminal end of an *Anisakis* larva. *A* anus, *DA* intestine, *DB* intestinal protrusion, *DO* thorn, *NR* nerve rings, *OE* oesophagus, *VB* protrusion of ventriculus, *VE* ventriculus

Further Reading

Mattiucci S et al (2015) Integrating *Anisakis* spp. parasites data and host genetic structure in the frame of a holistic approach for stock identification of selected Mediterranean Sea fish species. Parasitology 142:90–108

Nieuwenhuizen NE, Lopota AL (2013) *Anisakis* a food-borne parasite that triggers allergic host defences. Int J Parasitol 43:1047–1057

Sohn WM et al (2015) *Anisakis*: report of 15 gastric cases caused by *Anisakis* type 1 larvae and a brief review of Korean *Anisakis* cases. Korean J Parasitol 53:465–470

4.4.11 *Gnathostoma* Species (Gnathostomiasis)

1. **Name**: Greek: *gnathos* = jaw; *stoma* = mouth. Latin: *spina* = spike. English: Spiny bulbous worm.
2. **Geographic distribution/epidemiology**: In East Asia (especially in Thailand), but also in Central and North America *G. binucleatum*, *G. hispidum*, *G. lamothei*, *G. americanum*, *G. turgidum*, *G. procyonis* and *G. spinigerum*. Worldwide are several hundred thousands of humans infected.
3. **Biology, morphology**: The nematode *G. spinigerum* parasitizes within lumps formed inside of the intestinal wall of carnivores like dogs and cats (Figs. 4.52 and 4.53a, b). The eggs are excreted within the feces. Their further development can only start if they reach freshwater, since their first intermediate hosts are small crustaceans, while fish, but also reptiles, frogs, crabs and water birds, serve as second intermediate hosts. The **infection of humans**, pigs, cats and dogs occurs, when they ingest the 3–4 mm long larvae within raw or undercooked meat of the second intermediate hosts (Figs. 4.52, 4.53 and 4.54). These larvae, which possess a thorn at their apical pole, are unable to reach maturity inside humans, but start to creep around inside the stomach wall reaching a size of up to 1 cm × 1 mm and finally are found inside the skin,

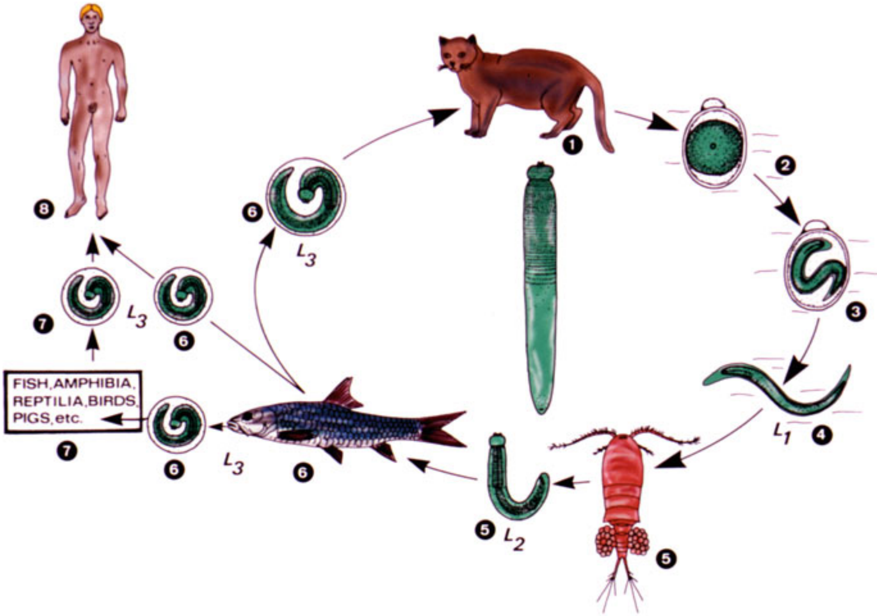


Fig. 4.52 Life cycle of *Gnathostoma spinigerum* inside its hosts. (**1**) Egg excreted by the final host cat. (**2**–**4**) Larva development inside the egg and hatch of the larva within water. (**5**) First intermediate host (small crustaceans, *Nauplius* sp.). (**6**) Fish are intermediate hosts 2, wherein the infectious larva 3 is developed. (**7**) Encysted larva inside intermediate hosts 2. (**8**) Humans as non-compatible hosts (larva 3 wanders through tissues)

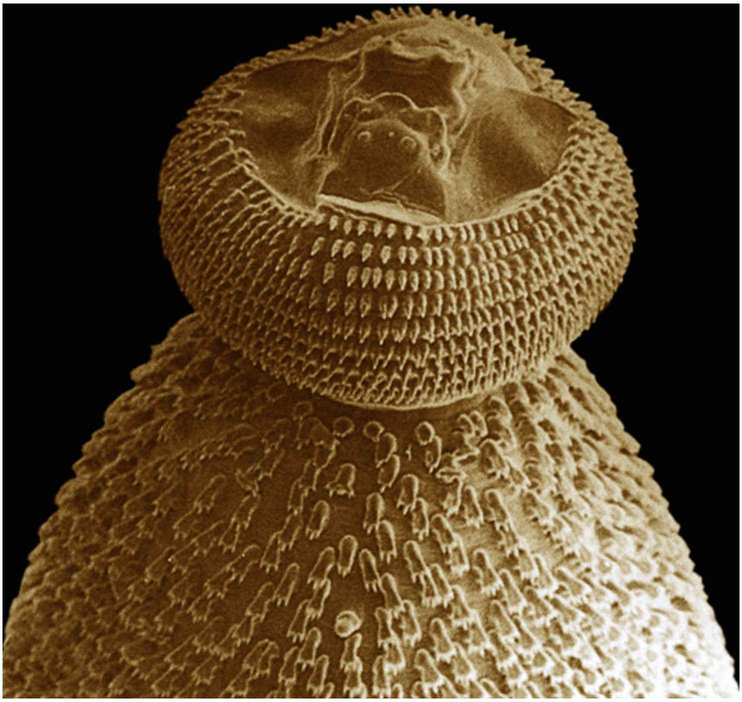


Fig. 4.53 Scanning electron micrograph of the anterior pole of an adult *Gnathostoma* worm. Note the differently sized scales sticking in the surface

where they induce wandering swellings of up to 3 cm in size (so-called **creeping eruptions**). If such larvae enter the brain, they may initiate there severe damages. In the case of their specific final hosts, however, they enter—after a phase of body wandering—again the intestinal wall of the intestine, where they reach maturity inside nodules and proceed copulation followed by egg production. The eggs are finally excreted in the feces. In humans, they do not reach maturity, so that no eggs are found in fecal examinations.

4. **Symptoms of the disease**: During the phase of the larval migration through the human body very unspecific symptoms occur. In cases of large amounts of wandering larvae, the blood picture shows similarities to a high-grade allergy, while in cases of brain invasion by *G. spinigerum* an eosinophilic encephalomyelitis was noted in post-mortem examinations.
5. **Diagnosis**: The diagnosis is difficult, since the symptoms are very unspecific and the persons mostly do not remember to have eaten potentially infected meat of fish. If the blood picture shows a high eosinophilia, leucocytosis and/or an eosinophilic pleocytosis, an infection by *Gnathostoma* specimens might be suspected, which then can be cleared by the help of serological methods such as ELISA or Western blot. However, cross reactions with other helminths are possible.

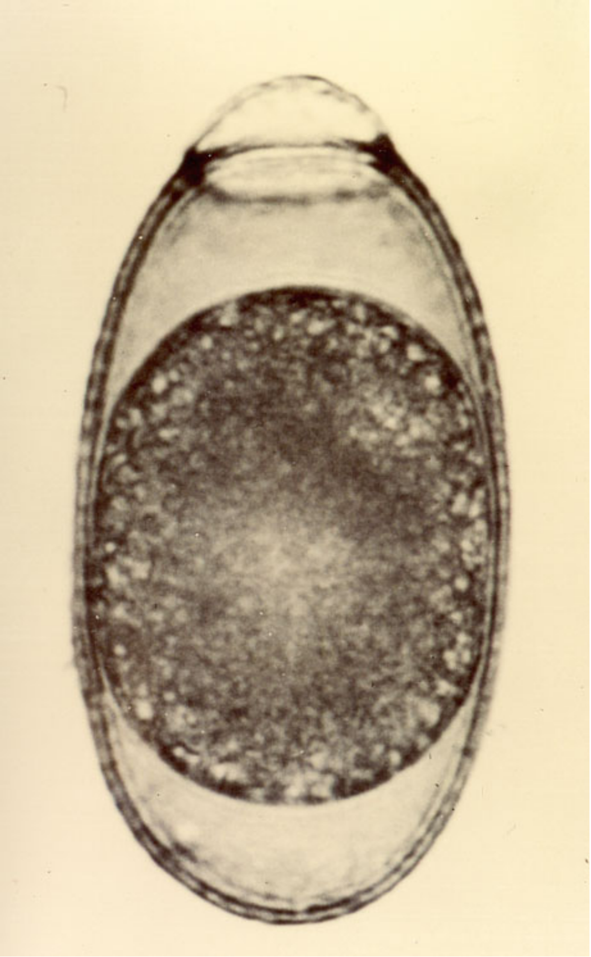


Fig. 4.54 Light micrograph of a typical egg of *Gnathostoma* sp. showing an anterior plug

6. **Pathway of infection**: Oral uptake of larvae within raw meat of fish and crabs or within undercooked meat of ducks, chickens, pigs, etc., which had the chance to ingest larvae 1 of this worm.
7. **Prophylaxis**: Avoid to eat raw fish or undercooked meat of animals which may have contact to water, wherein possible intermediate hosts 1 of *Gnathostoma* might live. Deep frozen meat of intermediate hosts, however, is safe.
8. **Incubation period**: 3–7 days.
9. **Prepatent period**: There is no formation of eggs inside humans.
10. **Patency**: Many months during migration through the human body.
11. **Therapy**: **Albendazole** (2 × 200 mg daily for 3 weeks) showed good clinical healing effects. Larvae seen during migration through eyes or within the skin should be removed surgically. In the case of a suspected brain invasion, corticosteroids should be administered additionally.

Further Reading

Diaz JH (2015) Gnathostomiasis: an emerging infection of raw fish consumption in *Gnathostoma* nematode-endemic and non-endemic countries. J Travel Med 22:318–324

Gaspar-Navarro J et al (2013) Description of advanced third-stage larvae of *Gnathostoma lamothei* from experimental hosts and contribution to its life cycle. Parasitol Res 112:169–175

Zambrano-Zaragoza JF et al (2012) Characterization of the humoral immune response against *Gnathostoma binucleatum* in patients clinically diagnosed with gnathostomes. Am J Trop Med Hyg 86:988–992

4.4.12 *Toxocara* Species (Toxocariasis)

1. **Name**: Greek: *toxon* = arch, bow; *kara* = head (=worms with a bended anterior end); *mystax* = beard; *catta* = cat. Latin: *canis* = dog. English: Dog roundworm.
2. **Geographic distribution/epidemiology**: Worldwide; many hundred thousands of humans are infected—many of them do not know it.
3. **Biology, morphology**: These roundworms (*T. canis*, *T. mystax*, syn. *T. cati*) of dogs and cats do not reach maturity inside humans and thus they do not produce eggs. They reach as larval stages a length of 1 mm up to 5 cm and migrate throughout the whole body. Thus, they are found as so-called **larvae migrans interna** and **L. m. visceralis** within many organs. If they wander through the subcutaneous tissues, protrusions of the skin appear called "creeping eruptions". The infection of humans occurs by oral uptake of larva-containing eggs excreted by dogs or cats and being placed in their fur or are found on the soil of playgrounds. The life cycle stages and eggs are depicted in Figs. 4.18, 4.55, 4.56 and 4.57.
4. **Symptoms of the disease (Larva migrans visceralis)**: During the migration phase of the larvae of the *Toxocara* species, unspecific symptoms occur such as fevers and a significant eosinophilia. The severity on the effects of such an infection depends on the amount of wandering larvae and of the penetrated organ. Thus, there are dysfunctions of the intestine, of the liver and of lungs besides damages of the nervus opticus (leading eventually to blindness). Brain and heart dysfunctions may lead to the death of heavily infected persons.
5. **Diagnosis**: Since parasitic stages are found neither in feces nor in urine and blood, serological methods have to be used for diagnosis of an infection. However, these tests (e.g. ELISA, IIFT) show only about 80 % of the infections. Thus, the grade of blood eosinophilia has to be considered in addition. In some rural populations of humans, seropositivity may reach 30 % (up to 70 %).

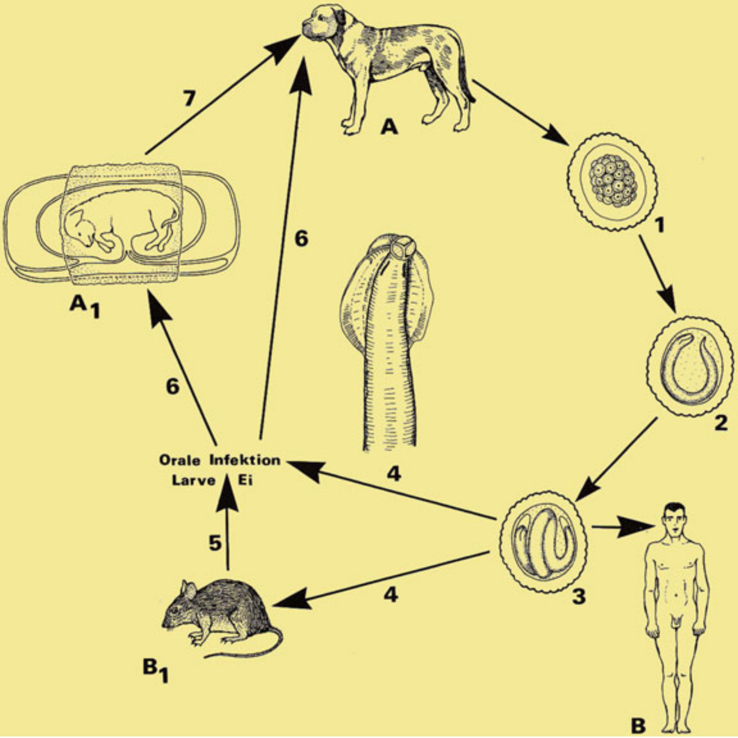
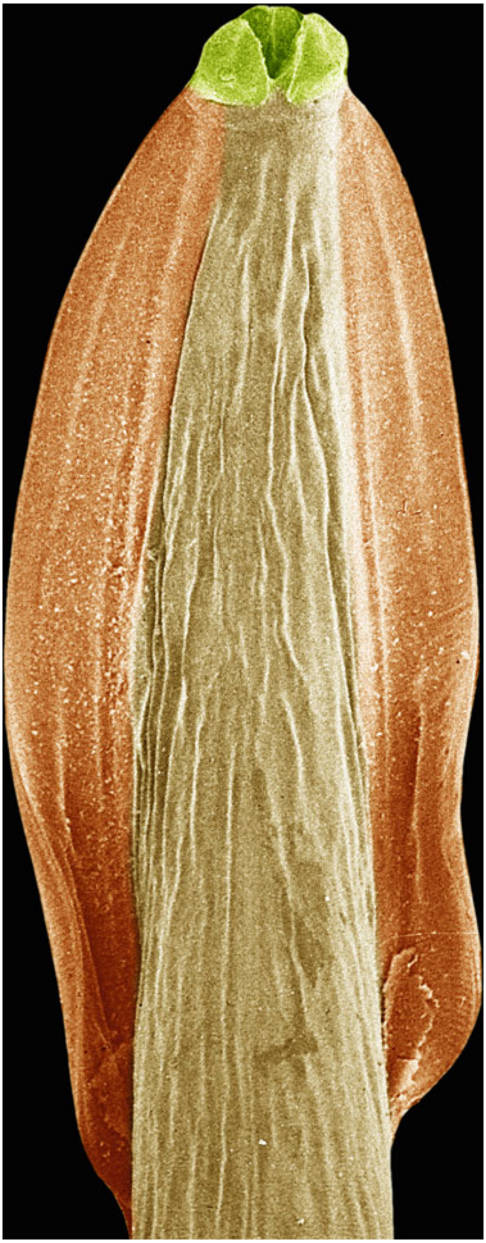


Fig. 4.55 Diagrammatic representation of the life cycle of the dog roundworm *Toxocara canis*. (**A**, **B**) Host types: (**A**): Final host; (**B**): Occasional host humans. (**B1**) = paratenic host (transport host). (**1**–**3**) Development: (**1**) Just excreted, thick-walled egg; (**2**) Egg containing the larva 1 (outside the body); (**3**) Egg containing larva 2 (outside the body); (**4**) If such a larva 2-containing egg is ingested by humans or by immune dogs, the larva 2 hatches in the intestine and starts migration inside their bodies as so-called **larva migrans**. (**5**–**7**) If non-immune dogs ingest larva-containing eggs (**4, 6**) or larvae-containing mice (**5**), the larvae reach after a heart–lung–trachea passage the intestine, where the worms become mature. However, even at a slow immunity of a female dog the larvae do not develop further inside its body and remain inactive in a waiting stage. In case the female dog becomes pregnant, the hormones of the dog stimulate the larvae, which then enter the unborn puppies, which thus are infected when just borne. Infections via the mother's milk are also common. This life cycle of *T. canis* shows the flexibility of its pathways of infection and how easily humans in the surroundings of untreated dogs may become infected

6. **Pathway of infection**: Oral uptake of larva-containing eggs of *Toxocara* eggs during playing on fecally contaminated playgrounds or by direct contact to fur of infected dogs and cats (Figs. 4.18 and 4.55).
7. **Prophylaxis**: Since about 20 % of the cats and dogs may excrete periodically worm eggs, their defecation on playgrounds of children must be prohibited. The sand within sandpits should be changed at least two times per year. Private sandpits should be covered during nights. Dogs and cats in the family should regularly become dewormed at intervals of 2–3 months.

Fig. 4.56 Scanning electron micrograph of the anterior end of an adult *T. canis* showing its alae (=wing-like anterior protrusions)



8. **Incubation period**: 2–3 weeks.
9. **Prepatent period**: Reproduction of the worm stages does not occur in humans.
10. **Patency**: Months are needed until the wandering larval worms are killed by the immune system inside of granulomas.

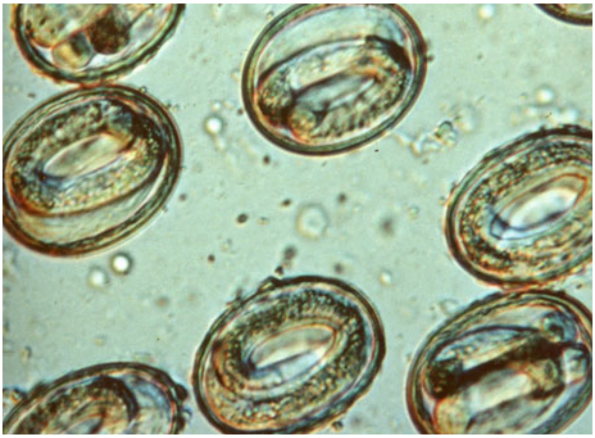


Fig. 4.57 Light micrograph of *T. canis* eggs containing an infectious larva

11. **Therapy**: The efficacy of anthelmintics is not completely proven. In cases with severe symptoms, a treatment trial using **tiabendazole** (Minzolum®2 × 25 mg/kg bodyweight) seems appropriate when given for 5–7 days. Also **diethylcarbamazine** has been used (dosages like in the case of filariae). **Albendazole** (10 mg/kg bodyweight daily for 5 days was shown to be as effective as tiabendazole. In cases of larva occurrence in the eyes, surgery is recommended—if the larva is situated at an unproblematic site. In any way, chemotherapy of wandering larvae may afford a simultaneous treatment with corticosteroids to minimize allergic reactions.

Further Reading

Antolova D et al (2015) Seroprevalence of human *Toxocara* infections in the Roma and non-Roma populations of Eastern Slovakia: a cross-sectional study. Epidemiol Infect 143:2249–2258

Borecka A, Klapec T (2015) Epidemiology of human toxocariasis in Poland – a review of cases 1978–2009. Ann Agric Environ Med 22:28–31

Heuer L et al (2015) Effects of *Toxocara* larvae on brain cell by in-vitro model assessment. Parasitology 142:1326–1334

4.4.13 *Dictyophyme renale* (Dictyophymiasis)

1. **Name**: Greek: *die* = two; *octos* = eight; *phyme* = living organism. Latin: *renalis* = belonging to kidneys. English: Kidney worm
2. **Geographic distribution/epidemiology**: Worldwide, however, only a few human cases of infections are reported.
3. **Biology, morphology**: *D. renale* belongs to the group of nematodes, which parasitize inside the kidneys of hosts like marine otters, foxes, dogs, cats, pigs

and rarely also humans. The adult worms reach as females an extraordinary size of 20–100 cm × 0.5–1.2 cm and 15–45 cm × 0.4–0.6 cm as males. They appear intensively red due to the fact that they engorge blood. The males are equipped with a protrusible hook (=spiculum), which is used to hold fast the female during copulation. In contrast to other nematodes, the females possess only a single ovarial cord. The 64–68 μm × 40–50 μm sized eggs are excreted in the 2-cell status within the urine of their hosts. Outside of the body a larva is developed, which hatches only if the egg has reached a water biotope and is ingested by a freshwater leech (first intermediate host). These leeches attach themselves to crabs, which are ingested by fish, which become second intermediate hosts. Inside these fish, the larva 3 is developed or even (after a long waiting time) the pre-adult stage. The infection of humans and other final hosts occurs during ingestion of raw or undercooked fish meat containing the infectious larvae. The pre-adult worms wander into the kidney (or occasionally also into the pleural or abdominal cavities), where they reach within 3–6 months maturity and may survive for 1–3 years.

4. **Symptoms of the disease**: Due to the large size of the worms, the kidney tissues are destroyed mechanically at many places, which leads to the fact that bloody urine is excreted (haematuria). Also secondary bacterial infections are common.
5. **Diagnosis**: Microscopically demonstrations of the eggs in the sediment of centrifuged urine.
6. **Pathway of infection**: Oral during uptake of raw or undercooked meat of infected fishes.
7. **Prophylaxis**: Fish meat should only be eaten cooked or after deep freezing.
8. **Incubation period**: 1 month.
9. **Prepatent period**: 3–6 months.
10. **Patency**: 1–3 years.
11. **Therapy**: Chirurgical removal of the adult worms from the interior of the kidneys and additional treatment with antibiotics to eliminate secondary bacterial infections.

Further Reading

Brand T (1957) Glycogen and lipoids in *Dictyophyme renale*. Z Tropenmed Parasitol 8:21–33

4.4.14 *Ternidens deminutus* (syn. *Triodontophorus deminutus, Globocephalus macaci*) (Ternidens Disease)

1. **Name**: Greek: *terna* = end; Latin: *nidificare* = nisting (=describes that the worm lives in the terminal region of the intestine); *deminutes* = the posterior end is tapering. English: African colon worm.

2. **Geographic distribution/epidemiology**: In regions of East Africa and South Africa and in the Congo basin, hundred thousands of humans are infected.
3. **Biology, morphology**: The adult females measure 12 × 0.6 mm and the males 9 × 0.5 mm and are mainly found in the colon of monkeys but also in humans (especially in people living in regions of Uganda and Zimbabwe). The eggs measure 60 × 40 μm and can be easily be mistaken for those of hookworms. Outside of the body the larva 1 hatches and reaches via two moults the infectious stage as larva 3. After ingestion of this larva via contaminated food, this larva develops into the adult male or female worm, which settles inside the colon being attached at the wall by the help of their head capsule.
4. **Symptoms of the disease**: Mostly rather unspecific intestinal dysfunctions and disturbances; in rare cases the lack of iron leads to an iron deficiency syndrome.
5. **Diagnosis**: Microscopically detection of the eggs that look similar to those of hookworms.
6. **Pathway of infection**: Oral by ingesting of larvae 3 on fecally contaminated plants and fruits.
7. **Prophylaxis**: Intensive cleaning and/or cooking of vegetables, which might have been contaminated by human or monkey feces.
8. **Incubation period**: Unknown.
9. **Prepatent period**: Unknown.
10. **Patency**: Unknown.
11. **Therapy**: Similar to hookworms (see Sect. 4.4.4).

Further Reading

Hemsrichart V (2005) *Ternidens deminutus* infection: first pathological report of a human case in Africa. J Med Assoc Thai 88:1140–1143

Kouassi RYW et al (2015) Diversity of gastrointestinal parasites in seven non-human primates of the Tai National Park, Côte d'Ivoire. Parasite 22:1–8

Schindler AR et al (2005) Definition of genetic markers in nuclear ribosomal DNA for a neglected parasite of primates, *Ternidens deminutus*. Parasitology 131:539–546

4.4.15 *Trichostrongylus* Species (Trichostrongyliasis)

1. **Name**: Greek: *thris*, *trichos* = hair; *strongylos* = rounded. English: Gastrointestinal hair worms.
2. **Geographic distribution/epidemiology**: Worldwide, about 10–20 million humans are infected (often without their knowledge).
3. **Biology, morphology**: These tiny worms reach a length of 3–9 mm and live in general in the upper intestinal tracts of carnivores being mostly deeply embedded into the mucosa. The females produce for 6–9 years eggs, which are

excreted in the morula stage and develop inside a larva 1 outside of the body. This larva hatches and develops via two moults the infectious larva 3. The infection of humans occurs by accidental ingestion of such larva 3 being attached, e.g., to vegetables. After two further moults, the adult stage is reached within about 25 days inside the human intestine.

4. **Symptoms of the disease**: The worms lead to destruction of the intestinal wall. Depending on the amount of worms, symptoms may be absent or severe abdominal pain may occur in cases of huge infections.
5. **Diagnosis**: Microscopically demonstration of the 75–90 μm × 40 μm sized unembryonated eggs, which can be obtained by the help of the flotation method. Mostly they do not contain more than 32 cells. Culture of feces will show the typical rhabditiform larvae 1.
6. **Pathway of infection**: Oral by uptake of free, sheathed larvae being attached to vegetables. Due to the absence of immunity, repeated infections are possible.
7. **Prophylaxis**: Intense cleaning of vegetables before eating in those countries, where human or animal feces are spread on fields.
8. **Incubation period**: 3 weeks.
9. **Prepatent period**: 3–4 weeks.
10. **Patency**: 5–8 years.
11. **Therapy**: Anthelmintics belonging to the groups of mebendazole, levamisole, pyrantel or bephenium, which are effective when applied in dosages similar to those used for hookworm treatment.

Further Reading

Gregory L et al (2015) Dried, ground banana plant leaves (*Musa* spp.) for the control of *Haemonchus contortus* and *Trichostrongylus colubriformis* infections in sheep. Parasitol Res 114:4545–4551

Khadijah S et al (2013) Soil moisture influences the development of *Haemonchus contortus* and *Trichostrongylus colubriformis* to third stage larvae. Vet Parasitol 196:161–171

Trapani F et al (2013) Histopathological, histochemical and immunohistochemical findings of the small intestine in goats naturally infected by *Trichostrongylus colubriformis*. Vet Parasitol 191:390–393

4.4.16 *Wuchereria bancrofti* (Lymphatic Filariasis)

1. **Name**: This nematode species was named honouring the two scientists Otto Wucherer (1820–1873) and Joseph Bancroft (1836–1894). English: Filarial worm.
2. **Geographic distribution/epidemiology**: Humid-warm regions in Africa, Asia and South America. Only 1 % of the transmitted larvae become adult worms.

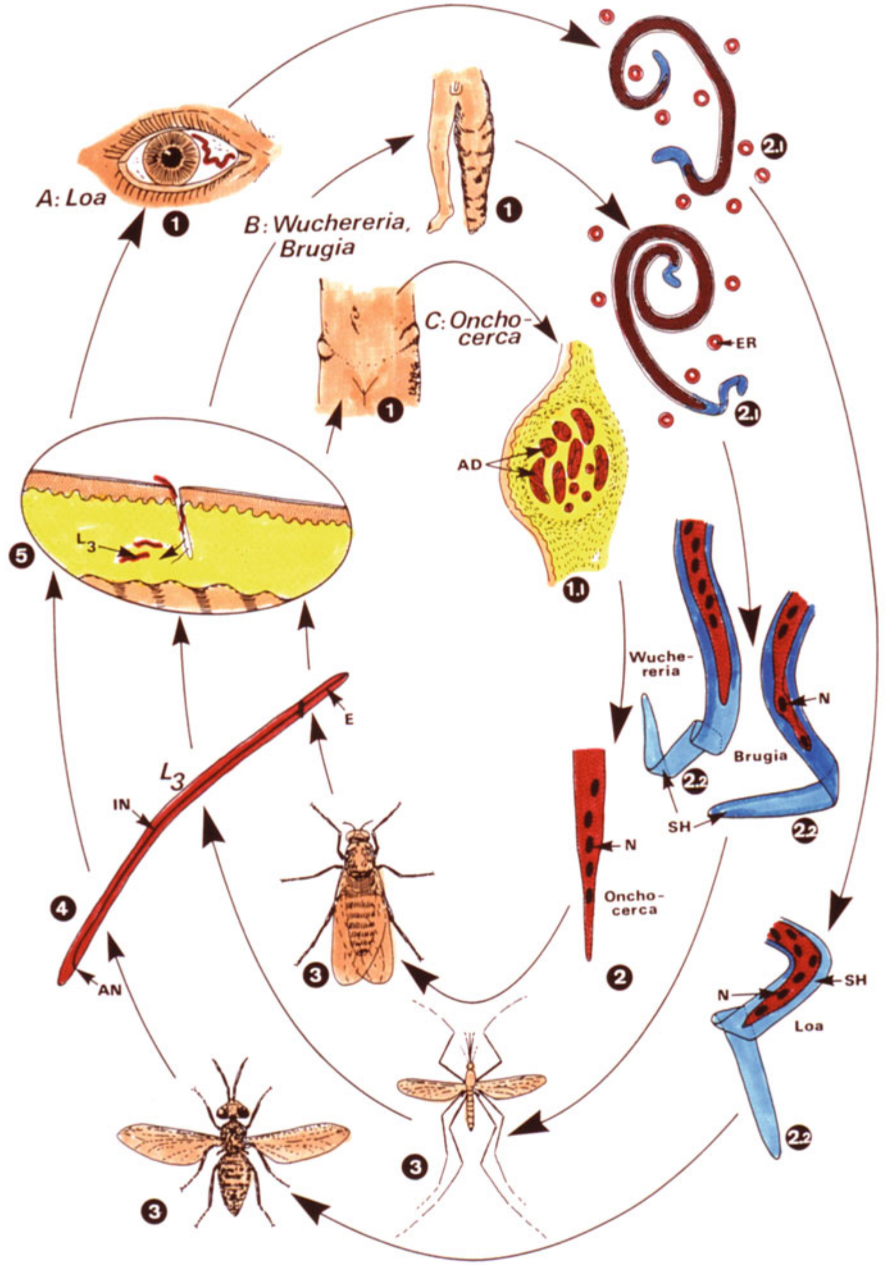
However, nevertheless about 100 million humans are actually infected by larvae producing adult worms.

3. **Biology, morphology**: The adult females reach a length of 10 cm and a width of only 0.3 mm, while males are much smaller (4 cm × 0.1 mm). They live inside the lymph vessels and in lymph nodes (Fig. 4.58). They need after being transmitted during blood sucking of their vector mosquitoes (species of the genera *Anopheles*, *Aedes* and *Culex*) about 1–2 years to reach maturity. After this initial phase and after repeated fertilizations, the females produce sheathed larvae for 6–7 years. These larvae measure 270–320 μm × 8–10 μm (Fig. 4.59a). They live for 6–18 months and appear periodically at ~10 o′clock p.m. in the peripheral blood of infected humans as a so-called **microfilaria nocturna**, so that then they can become ingested by nightly active female mosquitoes during their blood meal (Fig. 4.58). However, *W. bancrofti* has also subspecies, where the microfilariae appear also during daytime. Inside the mosquitoes, the larva 3 is developed within 6–20 days and after two moults. This 1.5 mm long stage is ready to become transmitted to a new human host (also monkeys may become infected). Since the larva 3 is too big to be transmitted within the saliva, it leaves actively the mouthparts of the mosquito during blood sucking, creeps down to the biting site and enters into the wound after the mosquito has retracted its mouthparts out of the wound.

   A subspecies of *Wuchereria bancrofti* (e.g. *W. b. pacifica*) occurs in Papua Guinea and in the South Pacific regions. The microfilariae of this species occur during the afternoon hours in the peripheral blood, so that especially *Aedes* species are used as vectors. In South America, another species has been described as *W. lewisi*, but it is not yet clear whether it is an own species. If patients become infected in Asia and go back to Europe, the microfilariae appear after a short time of adaption also at 10 p.m. European time in the peripheral blood.

   All *Wuchereria* species and subspecies contain bacterial endosymbionts belonging to the genus *Wolbachia*, which deliver substances that are essential for the worms. Thus, application of doxycycline is a new method to control *Wuchereria* infections.

4. **Symptoms of the disease (Filariasis)**: Symptoms of disease start only after an incubation time of 4–8 months after the bite of an infected mosquito. This very long incubation period is important and has to be considered, when unclear symptoms occur in persons which had stayed even long ago in endemic regions. The symptoms of disease are mainly based on reactions against the adult or growing worms and are not due to the presence of microfilariae, which live only for a few months. The **first symptoms** of a filariasis due to *W. bancrofti* occur earlier than the microfilariae can be diagnosed inside the blood. There occur unspecific fever phases and repeated swellings of lymph nodes in the regions of the groins and armpits besides signs of a lymphangitis (=inflammations of lymph vessels along the legs and arms or in the genital region) accompanied by reduction of sensitivity of legs and arms. As soon as microfilariae enter the cerebrospinal fluid, symptoms of encephalitis occur.


A: Loa
1
B: Wuchereria, Brugia
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C: Onchocerca
1
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3
3
Wuchereria
N
Brugia
2.2
SH
2.2
N
Onchocerca
2
N
SH
Loa
2.2

Fig. 4.58 Diagrammatic representation of the life cycles of human filariae. (**A**) → *Loa loa* adult worms (= → macrofilariae: male 3.5 cm, female 7 cm) wander subcutaneously and may pass the anterior chamber of the eye (**1**). (**B**) → *Wuchereria bancrofti* adults (male 4 cm, female 10 cm) and → *Brugia malayi* adults (male 3 cm, female 9 cm) live in lymph vessels and lead to a late-stage disease called → elephantiasis tropica (**1**). (**C**) → *Onchocerca volvulus* adults (male 2–4 cm, female 70 cm) are knotted together in groups in the subcutaneous tissues. Because of host reactions these groups are encapsulated, leading to palpable → nodules (**1**). In sections of these nodules

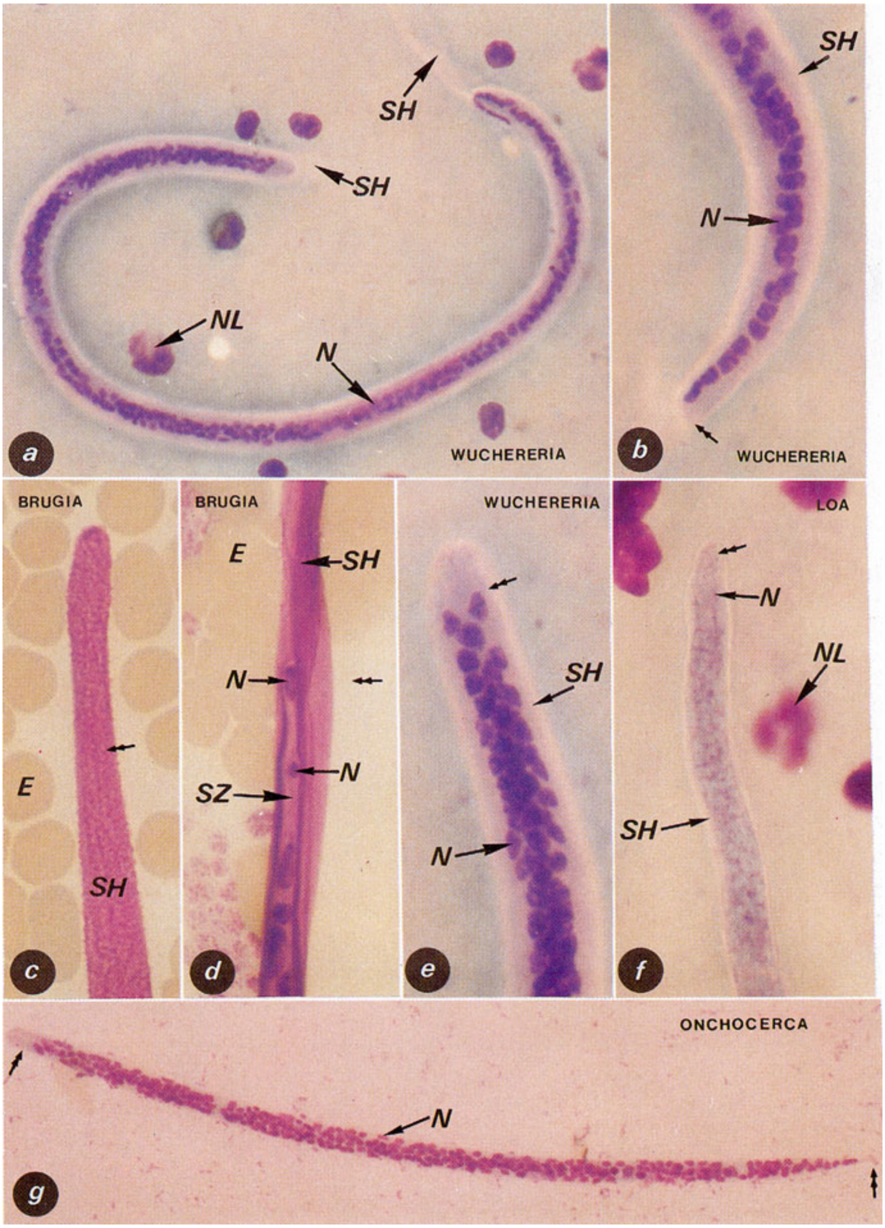
Late symptoms occur mostly after long-lasting infections and presence of microfilariae. They are characterized by characteristic blockings of the lymph fluid, occurrence of swellings of the legs and arms and eventual appearance of **chyluria** (=glooming of the urine due to entering of lymph fluid into the bladder). As very late symptoms (after years, when microfilariae are no longer present), signs of the so-called **elephantiasis tropica** occur, which are characterized by enormous swellings of the legs, arms, breasts of women or the scrotum of males.

5. **Diagnosis**: The basic diagnostic feature of an infection with filarial worms is the occurrence of the microfilariae. In the case of *W. bancrofti*, the microfilariae have a size of 270–320 μm × 6–8 μm, are sheathed and occur mainly between 10 p.m. and midnight in the peripheral blood (Fig. 4.59a, b, c). Mixed with citrate the obtained blood can be stored until the next morning for microscopical examination. If it is not possible to get blood in the evening hours, the occurrence of microfilariae can be provoked also during daytime by ingestion of 50–100 mg diethylcarbamazine (so-called Mazzotti test). About 30–60 min after this application, the microfilariae will appear in the peripheral blood and can be seen in microscopical inspections. **Attention**: There is a high-grade danger of an anaphylactic shock reaction in the case that there are infections with larvae of *Onchocerca volvulus* or *Loa loa*.

   Inspecting fresh non-fixed blood, the microfilariae can easily be detected due to their typical winding movements. However, for an exact determination it is needed to stain them in smear preparations by the help of the Giemsa stain or by use of haematoxylin according to Delafield. Enrichment methods are

   (a) Thick droplet (however, the species differentiation is poor)

Fig. 4.58 (continued) coiled adults are seen (**1.1**). Microfilariae may induce →blindness. (**1**) Visible signs of disease. (**2**) Microfilariae; the shape (**2.1**), structure (**2**, **2.2**) and diurnal occurrence are species specific: they may or may not be sheathed (**2.2**); their terminal nuclei have a species-typical appearance (**2**, **2.2**); they can be found in blood vessels (→*Loa*, →*Brugia*, →*Wuchereria*) or in lymphatic gaps (→*Onchocerca*); their occurrence in the peripheral blood can be periodical (*Loa*, during the day; *Wuchereria* during the night; some subperiodic strains also exist) or may not be (*Onchocerca,* always present, but in lymph vessels). (**3**) Intermediate hosts: Depending on the periodic appearance of microfilaria in the host's skin, insects with different biological behaviour are involved as → vectors. Daytime-feeding vectors (deerflies, →*Chrysops* species, →blackflies, →*Simulium* spp.) transmit *Loa loa* or *Onchocerca volvulus*, whereas night-feeding → mosquitoes (→*Aedes*, →*Culex*, →*Anopheles*) may be vectors of the nocturnal strain of *Wuchereria* and *Brugia*. When microfilariae are ingested by intermediate hosts during the blood meal, they penetrate the intestine and enter the abdominal cavity and the thoracic muscles. After a → moult the L_2 is formed, which has a stumpy shape (sausage stage). Another moult finally leads to the filariform infectious L_3. (**4–5**) L_3 reach a length of about 1.5 mm and migrate to the → proboscis, from which they escape when the vector is feeding. They enter the skin through the wound channel made by the biting insect (**5**, *arrow*). Inside the final host (man) the larvae migrate until they reach their favourite site of location, where they mature (after another 2 moults) within 1 year (prepatent period; →Nematodes). *AD* adult worms (in section), *AN* anus, *E* oesophagus, *ER* erythrocyte, *IN* intestine, *L3* third larval stage, *N* nuclei (their arrangement at the poles of microfilariae is species specific), *SH* sheath (→eggshell)


SH
SH
NL
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a
WUCHERERIA
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LOA
N
NL
SH
f
ONCHOCERCA
N
g

Fig. 4.59 Light micrograph of Giemsa-stained microfilariae (=larvae 1 of the filarial worms) inside human blood (**a–f**) or in the lymph (**g**). (**a**) *Wuchereria bancrofti*, total microfilaria. (**b**) *W. bancrofti*: posterior end of a microfilaria: The nuclei do not reach until the terminal end (*arrow*). (**c**) *Brugia malayi*: The sheath (SH) is strongly stained and appears granulated (*double arrow*). (**d**) *Brugia malayi*: posterior pole. One nucleus is situated exactly at the terminal pole (*double arrow*) and another one in some distance. (**e**) *W. bancrofti*: anterior end; a nucleus-free region has the size of the width of the larva. (**f**) *Loa loa:* although the worm is stained, coloration is

(b) Microhaematocrit method
(c) Membrane filtration
(d) Knott's enrichment technique (centrifugation for 10 min at 3000 turns per minute of 3 ml citrate or EDTA blood after being mixed with 6 ml of a 2 % watery formalin solution

1. **Membrane filter method**

   3–5 ml anticoagulated blood (being haemolysed by the help of aqua dest., teepol and saponin) were pressed by the help of a syringe through a polycarbonate filter with 3 μm pores (see also *Schistosoma haematobium*, Sect. 4.2.1). After this, a NaCl (0.9 %) solution is pressed several times followed by drying just by air. After this procedure, the filter paper is placed onto a glass slide, stained by the help of a Giemsa solution and examined microscopically.
2. **Knott's enrichment method**

   1–10 ml EDTA blood are mixed with the tenfold amount of a 2 % watery formalin solution, centrifuged for 10 min at 1500 g. After this procedure, the sediment is investigated quantitatively by the help of a microscope.

Microfilariae also become demonstrated besides in blood also in punctions of hydroceles and lymph varices, in the urine (e.g. in the case of chyluria) as well as in biopsy material obtained from skin, muscles, internal organs and (rather rarely) in fluid. Occasionally, sections of adult worms were seen when obtained during surgery due to other reasons. By the help of different serologic methods (ELISA, IFT, etc.), antibodies against homologous and heterologous antigens of filariae can be shown. However, there are also cross reactions possible with other helminthiases such as echinococcosis, trichinosis or other intestinal nematode infections. However, serology is the only means for a diagnosis during the long prepatent periods and during the long-lasting late phases of filariasis (with very few or no microfilariae). This is especially true in the case of the **tropical pulmonary eosinophilia syndrome**, where high antibody titres are the most significant indicators.

6. **Pathway of infection**: Percutaneous infections occur during the bite of nightly active, blood sucking females of the genera *Anopheles* and *Culex*. *Wuchereria* var. *pacifica*, which shows no nightly periodicity in the appearance of

◀

Fig. 4.59 (continued) poor; thus, the nuclei can only hardly be seen; however, they are found also at the anterior pole. (**g**) *Onchocerca volvulus*. Total of a microfilaria obtained from a lymph vessel. The anterior and posterior regions are clearly free from nuclei. *E* erythrocyte, *N* nucleus, *NL* nucleus of a leucocyte, *SH* sheath, *SZ* tail microfilariae inside the peripheral blood, is transmitted by day-active *Aedes* females. In all cases, however, the rather large larvae 3 pass (during a blood sucking phase) the vector's mouthparts and enter the wounds at the biting sites. There are mostly transmitted only 3–4 larvae during each blood sucking act. Infections, however, can be repeated many times, since immunity is not developed, so that after a longer stay in an endemic region also large amounts of worms can be acquired.

7. **Prophylaxis**: Avoidance of bites of mosquitoes by the help of mosquito nets during sleeping and application of repellents like Viticks® or Autan® when staying outside of houses.
8. **Incubation period**: 3–16 months.
9. **Prepatent period**: 7–24 months.
10. **Patency**: 8–10 years, although adult worms were found that lived for up to 18 years. This shows that their fertility ends earlier. These findings, however, were obtained in subperiodic strains, which are transmitted by mosquitoes of the genera *Mansonia* and *Coquillettidia*.
11. **Therapy**: For many years, the drug of choice was **diethylcarbamazine** (starting with 50 mg per day increasing to 3 × 150 mg; 3 × 2 mg/kg bodyweight per day for 2–3 weeks; maximal dose 72 mg/kg bodyweight). In cases of allergic reactions, salicyl preparations and antihistamine compounds or even corticosteroids were given. However, this treatment killed mostly only about 50 % of the adult worms. Later **ivermectin** was used, which did not kill the adults but led to their sterility for about 1 year. Thus, treatment has constantly repeated. **Most recent treatment approaches** yield on the killing of the symbiotic bacteria of the genus *Wolbachia*, which are essential for the adult *Wuchereria* worms. According to Prof. Hörauf (Bonn, Germany), a dosage of 200 mg **doxycycline** per day for 4–6 weeks led to a slow death of about 85 % of the adults without shock reactions, which are rather common in the case of using diethylcarbamazine (DEC).

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4.4.17 *Brugia malayi* (Lymphatic Filariasis)

1. **Name**: This species was named honouring the scientist Brug, who described this worm with Lichtenstein in 1927 and according to the region where it was first detected. English: Malayan filarial worm.
2. **Geographic distribution/epidemiology**: Humid-warm regions in Sri Lanka, India, East Pakistan, North and South of East Asia; at least 50 million humans are infected.
3. **Biology, morphology**: There are principal similarities to *Wuchereria bancrofti*. However, also some differences occur:
   - (a) Adult worms are smaller: ♀ 6 cm × 0.2 mm; ♂ 3 cm × 0.1 mm and the microfilariae are already produced 3 months after infection.
   - (b) The microfilariae are somewhat smaller (180–250 × 5–6 µm) and have a significant different arrangement of the nuclei at the terminal end (Fig. 4.59c, d).
   - (c) Daily occurrence of the microfilariae: nocturnal type like *W. bancrofti*.
   - (d) Transmission exclusively by nightly active mosquitoes.
   - (e) Elephantiasis symptoms occur mainly along the legs and only rarely along the urogenital system.
   - (f) *B. malayi* also infects dogs, cats and wild living mammals besides humans.

   Whether *Brugia timori*, which is found on the Indonesian Island named Timor, is clearly a different species is not yet decided. The sheathed microfilariae are also from the nocturnal type and measure 325 µm × 6 µm and thus are considerably larger than those of *B. malayi*. The transmission of *B. timori* microfilariae occurs by bites of the nightly active females of the species *Anopheles barbirostris* (Figs. 5.78 and 5.79)—however, also other mosquito species may be involved.
4. **Symptoms of the disease**: Early signs are lymphangitis and lymphadenitis being visible mainly along the legs and only rarely along arms or mammae, but never in the scrotum. The finally occurring elephantiasis is mainly seen in the legs below the knee reaching double diameters than normal.
5. **Diagnosis**: Microscopically determination of the nightly in the peripheral blood appearing microfilariae (Fig. 4.59c, d).
6. **Pathway of infection**: Percutaneously during bloodsucking of nightly active mosquitoes of the genera *Mansonia* and *Anopheles*, while *B. timori* is transmitted by *A. barbirostris*. The development inside the mosquito takes about 6–7 days.
7. **Prophylaxis**: Avoidance of bites of mosquitoes by application of repellents (Viticks®, Autan®) and by sleeping below insecticide-impregnated bed nets.
8. **Incubation period**: *B. malayi*: 30–60 days; *B. timori*: 60–90 days.

9. **Prepatent period**: *B. malayi*: 50–90 days; *B. timori*: 60–90 days.
10. **Patency**: 8–10 years.
11. **Therapy**: See *Wuchereria bancrofti* (Sect. 4.4.16). Mostly the treatment period can be reduced to 1–2 weeks using a total dose of 36 mg **diethylcarbamazine** per kg bodyweight. In the case of the use of **doxycycline,** 100 mg/day for 6 weeks was shown to be effective.

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4.4.18 *Loa loa* (Loiasis)

1. **Name**: African name originating in Angola. English: Eye filarial.
2. **Geographic distribution/epidemiology**: Humid and warm regions exclusively in Equatorial Africa between 10° North and 5° South, especially in coastal regions of the gulf of Guinea; about 20–25 million humans are infected.
3. **Biology, morphology**: The adult worms (also called wandering filariae) live up to 12 years especially inside the subcutaneous tissues of humans; however, they are also found in body cavities and pass also rather commonly the eye (eye filaria). The females measure about 7 cm × 0.5 mm, while the males reach only a size of 3.5 cm × 0.4 mm. These worms reach within 1–4 years after infection maturity, so that only after a rather long time after an infection microfilariae can be diagnosed. These microfilariae measure 260–320 μm × 8 μm and appear during daytime (maximum between 10 a.m. and 1 p.m.) inside peripheral blood system (thus they are described as “**microfilaria diurna**”). The adult female worms are able to produce up to 20,000 (**!**) microfilariae per day. Vectors are tabanid flies of the genus *Chrysops* (*C. dimidiata*, *C. silacea*, *C. longicornis*). Inside these bloodsucking insects, the larvae reach after two moults within 8–12 days the stage 3, which is transmittable (Figs. 4.58 and 4.59f).

4. **Symptoms of the disease**: After a rather long incubation period of 6–17 months, the first symptoms of disease occur, which in general, however, are always related to the skin, subcutis and the eyes and are apparently due to allergic reactions on excreted remnants of the metabolism of the worms. Very significant are the so-called **calabar swellings** (also called Cameroon swellings), which are oedemas with diameters of 1–10 cm that occur along the arms or in the face. These oedemas disappear after 2–3 days, but others appear at other places. As further symptom, a typical **skin itching** has been reported by a high percentage of patients. During the also rather common passage of the adult worms through the eye (Fig. 4.60), intense lacrimation occurs accompanied by a feeling of burning and itching. On the other hand, microfilariae may enter the cerebrospinal fluid and thus may induce symptoms of encephalitis.
5. **Diagnosis**: The most significant method is the diagnosis of the microfilariae inside the peripheral blood. If the blood is taken between 10 o'clock a.m. and 2 p.m., the so-called Mazotti test by application of maximal 25 mg diethylcarbamazine (DEC) should only be done in cases when general symptoms exist but no larvae are seen in blood smears, since the risk of severe anaphylactic reactions exists. Diagnosis of an existing infection becomes also confirmed, if wandering worms are seen inside the eyes, where they stay, however, mostly only for a short while.

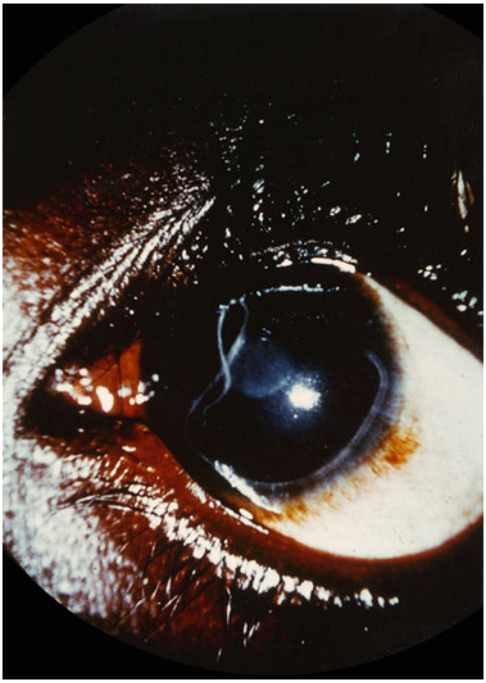

Fig. 4.60 Macrophoto of the eye of a patient showing an adult worm of *Loa loa* on its eye passage

Antibodies can be proven in most patients in high concentrations as it is the case in *Wuchereria bancrofti*. Furthermore, in most cases a high-grade blood eosinophilia was proven.

6. **Pathway of infection**: Percutaneously during bites of the so-called mango flies = tabanids of the genus *Chrysops* (see Fig. 5.95).
7. **Prophylaxis**: Use of repellents (Viticks®, Autan®) to avoid bites of insects.
8. **Incubation period**: 6–17 months.
9. **Prepatent period**: 6 months up to 4 years.
10. **Patency**: 4–17 years.
11. **Therapy**: Like in the case of *Wuchereria bancrofti* (Sect. 4.4.16): **diethylcarbamazine** (DEC) treatment for 3–4 weeks with a total dose of 125 mg/kg bodyweight. In contrast to the quick effects on the killing of the microfilariae, the adults die only after some time and up to 50 % may even survive. Therefore, it is often needed to repeat the treatment several times. Although the treatment dose should only slowly be increased, a high-grade microfilaraemia may lead to severe allergic reaction, which may become life-threatening due to anaphylactic shocks or encephalitic syndromes. These reactions can be treated with salicylates, antihistamines or even by the application of corticosteroids. In cases of a density of more than 25 microfilariae per μl blood, the application of corticosteroids is needed already before the anthelmintic treatment (e.g. 3 × daily 1–2 mg betamethasone). **Mebendazol** or **albendazol** (200–500 mg daily for 1–2 months) or **ivermectin** (1 × 0.3–0.4 mg/kg bodyweight) are also very effective; however, the effects on adult worms are still under discussion. Thus, it is urgently recommended to repeat the treatment after several controls of the parasitaemia of the microfilariae. Since *Loa loa* worms do not contain bacteria of the genus *Wolbachia* (or similar ones), a doxycycline treatment has no effects.

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4.4.19 *Onchocerca volvulus* (Onchocerciasis)

1. **Name**: Greek: *onkos* = swelling, node; *kerkos* = tail. Latin: *volvulus* = rolled in. English: Skin worm, nodule worm.
2. **Geographic distribution/epidemiology**: This worm is spread in the nearness of quickly floating creeks and rivers in Africa (Northern border: Senegal, Sudan, Ethiopia; Southern border: Angola, Tanzania), Yemen; in Central and South America (focally in South Mexico, Guatemala, Colombia, Brazil). About 50 million humans are infected and about 10 million blinded.
3. **Biology, morphology**: In humans, subepithelium regions contain 5–6 cm sized nodules of adult worms mostly consisting of several females which reach a length of 25–70 cm by 0.4 mm in diameter. The males are very small and reach mostly only a length of 4 cm. The males migrate through the body surface of infected humans on their search for females. The nodules containing several adult or growing females can be seen protruding on the surface of humans (Figs. 4.58, 4.61 and 4.62). The females produce after repeated fertilization for up to 15 years many of the non-sheathed microfilariae measuring about

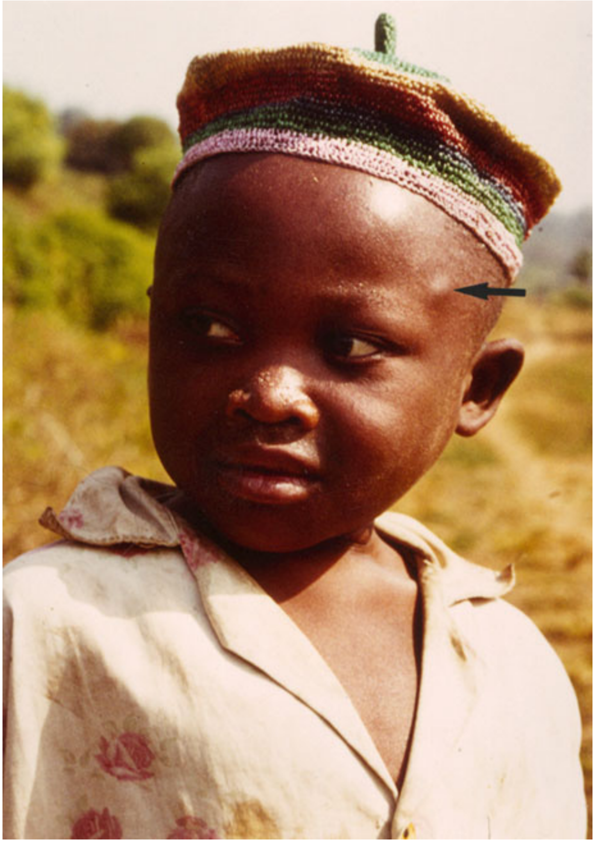

Fig. 4.61 Photo of an African child showing a progressing nodule (*arrow*) filled by females of *Onchocerca volvulus*

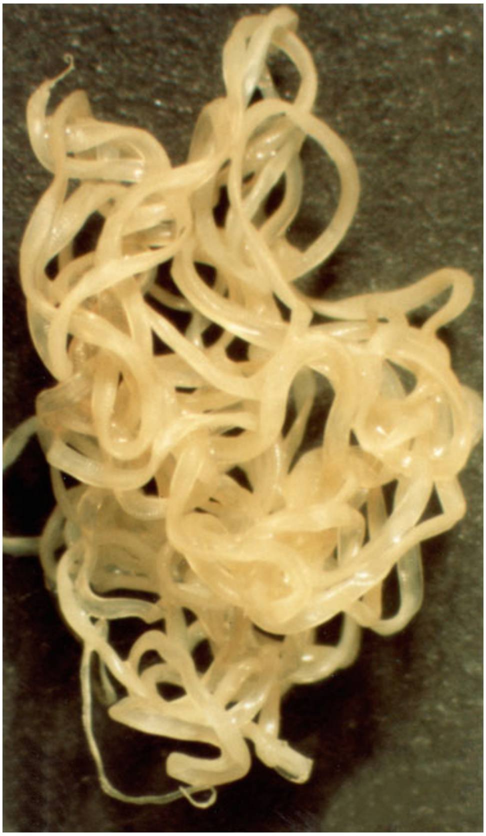

Fig. 4.62 Photo of females of *Onchocerca volvulus* after digestion of a skin nodule obtained from an African patient

310 µm × 6–9 µm (Fig. 4.59g), which migrate into the peripheral lymph vessels, but also into the eye, into the saliva glands and in the urine. These larvae are constantly—and not periodically like those of *Wuchereria*, *Brugia* or *Loa*)—available for bloodsucking insects in the periphery of a host's body. The microfilariae of *O. volvulus* can be morphologically differentiated from those of *Mansonella perstans* and other microfilarian species. The microfilariae of *O. volvulus* are transmitted during daytime by bloodsucking females of the genus *Simulium* (Figs. 5.74 and 5.75). After the microfilariae have been ingested, they penetrate and pass the intestinal wall and enter the muscles of the thorax, where within 6–8 days and after two moults the larva 3 is ready to become transmitted to another host. The infection of humans occurs, while the larvae 3 leave the mouthparts of the female *Simulium* fly and enter actively into the deepening of the biting site. Inside the subepithelial tissues of humans, the penetrated worm stages reach maturity (after two moults) within 9–14 months.

4. **Symptoms of the disease (Onchocerciasis, river blindness, Robles' disease)**:
   (a) **Nodules**:

Not before 4 months after infection (mostly after 1–2 years) the first touchable lumps can be noted, which may reach diameters of up to 6 cm and appear like fibromes (Fig. 4.61).

(b) **Chronic dermatitis**:

This symptom is accompanied by severe itching as a follow-up of the wandering activity of males and due to huge numbers of peripherally situated microfilariae in the lymph system. In the case of long-lasting infections, alterations of the skin are common and occur as sclerodermia, xerodermia, depigmentation and/or as a strong wrinkling of the skin (e.g. formation of so-called "hanging groins"). The symptom of the so-called **sowda** occurs very often in infected people in Yemen or focally in Cameroon. Sowda appears as a locally concentrated skin region characterized by hyperpigmentation and a papula-rich dermatitis.

(c) **Disease of the eyes**:

As a consequence of the penetration of the typical non-sheathed microfilariae into the eye symptoms of conjunctivitis, sclerotizing keratitis, iridocyclitis, chorioretinitis and "opticus atrophia" occur. After several years of repeated entering of such larvae, complete blindness may be induced (Fig. 4.63). This peculiar blindness is described as **river blindness** which hits still today about 10–25 % of the about 40 million infected humans.

5. **Diagnosis**: Microscopically demonstration of the microfilariae (Fig. 4.59g) obtained by the help of so-called skin snips. The 2–3 mm sized pieces of the cut-off skin were placed into a 37 °C warm, 0.85 % NaCl solution and exposed for 1–4 h. After centrifugation of the salt solution, the sediment contains the microfilariae (if present), which then can be coloured by Giemsa stain. In cases of a supposed presence of microfilariae inside the eyes, the patient is placed head down for some minutes. Afterwards the sinking microfilariae can be

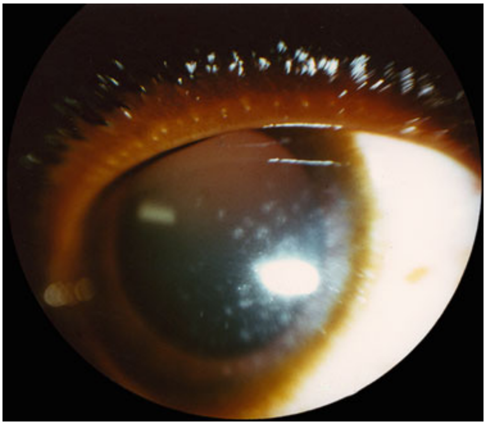

Fig. 4.63 Photo of a human eye (filled with *Onchocerca volvulus* larvae) in a late stage just prior to get fully blinded

observed during an eye inspection of so-called spot lamp used in ophthalmology.

Serologic diagnosis of onchocerciasis is difficult, since there are cross reactions with other worm groups. However, ELISA and the LATEX-agglutination test give good results, but are unfortunately not everywhere available.

6. **Pathway of infection**: Percutaneously by biting activity of simulids (e.g. *Simulium* species), which have a very short development phase of 15–20 days, so that sometimes masses of them attack humans and their animals (Figs. 5.72, 5.73, 5.74 and 5.75).
7. **Prophylaxis**: Avoidance of insect bites in endemic regions by use of icaridin-containing repellents such as Autan® and Viticks®.
8. **Incubation period**: 3–4 months.
9. **Prepatent period**: 9–30 months.
10. **Patency**: 10–16 years.
11. **Therapy**: Drug of choice is **ivermectin** (1 × 150–200 mg/kg bodyweight) due to its easy use and absence of side effects. It acts slowly, but only on microfilariae and not on adult worms. Therefore, treatment must be repeated at intervals of 12 months. This drug and its effective compound were detected by Prof. Dr. Omura (Kitasato-University, Tokyo), who received the Nobel Prize in the year 2015 for this finding. Ivermectin is today worldwide one of the most used anthelmintics in the treatment of animal nematodes. Thus, the producers of this drug offer it for free to people endangered by onchocercosis. However, yearly repeated use is needed, since the adult *Onchocerca* worms—in contrast to adults of other nematodes—are not killed by ivermectin. **Diethylcarbamazine** (DEC) acts also only against microfilariae, but has a higher risk of allergic reactions and may endanger eye functions. Thus, DEC should only be given when ivermectin is not available: starting by application of 25 mg (as in the case of *Loa loa*) and increasing until 2 × daily 100 mg—children 1–2 mg/kg bodyweight. **Application period of DEC**: 14 days and repetition all 6–12 months.

    Results of Turner et al. (2010) showed that **doxycycline** (200 mg/day for 6 weeks) introduced sterilization of the female worms, since the included *Wolbachia* bacteria are killed.

    Adult worms can (actually) only be killed by use of suramin, which, however, is very toxic, so that its use is rather restricted on special cases. The dosage given once a week for 6 weeks should be constantly increased as follows: 0.2, 0.4, 0.6, 0.8, 1 and 1 g.

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4.4.20 *Mansonella* Species (Mansonelliasis)

4.4.20.1 *Mansonella perstans* (syn. *Dipetalonema, Acanthocheilonema*)

1. **Name**: This species obtained its name honouring the English scientist Patrick Manson (1844–1922) and by using the Latin word *perstare* = existing. English: American body cavity filarial.
2. **Geographic distribution/epidemiology**: Humid and warm regions in West and Central Africa and focally on Caribbean islands as well as in South and Central America. The number of infected persons should be close to 40 million persons.
3. **Biology, morphology**: The thread-like adult worms measure as females 8 cm × 0.2 mm and as males 4.5 cm × 0.06 mm. They are parasitizing inside body cavities of humans and primates (e.g. gorillas). The microfilariae produced by female worms are non-sheathed and measure 200 μm × 5 μm. They appear as well at daytime as during the night in the peripheral blood in the same concentrations and are transmitted by the females of midges (e.g. *Culicoides*) species (Figs. 5.79 and 5.80). After a development period of 7–9 days, the infectious larva 3 is ready to be transmitted during a blood meal. Due to the lack of a developing immunity, repeated transmissions may lead to huge numbers of worms inside human bodies.
4. **Symptoms of the disease**: In most cases, clinical manifestations are rather low grade. However, skin symptoms (=oedemas = so-called **calabar swellings**), urticaria, itching and abdominal pain have been reported. In most cases, however, a well-defined eosinophilia occurs (as in other filariasis).
5. **Diagnosis**: Microscopical demonstration of the unsheathed microfilariae in Giemsa-coloured smear preparations. In order to differentiate this, not very pathogenic species from those with a high destructive impact such as *Wuchereria bancrofti* or *Loa loa* is needed to obtain clear microscopical preparations, since *M. perstans* microfilariae are **not** surrounded by a sheath, while those of *Loa loa* and *W. bancrofti* are sheathed.

6. **Pathway of infection**: Percutaneously during blood sucking of midges.
7. **Prophylaxis**: Avoidance of insect bites by use of repellents.
8. **Incubation period**: 36 weeks.
9. **Prepatent period**: 36 weeks.
10. **Patency**: 1–2 years.
11. **Therapy**: In general not needed; however, compounds such as diethylcarbamazine, DEC, mebendazole, **ivermectin** and **doxycycline** show similar effects (at least in several strains) as in the more pathogenic filarial species.

Further Reading

Bain O et al (2015) Review of the genus *Mansonella* Faust, 1929 sensu lato (Nematoda: Onchocercidae), with description of a new subgenus and new subspecies. Zootaxa 11:151–193

Mourembou G et al (2015) *Mansonella*, including a potential new species, as common parasites in children in Gabon. PLoS Negl Trop Dis. doi:10.1371/journal.pntd.0004155

4.4.20.2 *Mansonella ozzardi* (Mansonelliasis)

1. **Name**: The genus was named honouring the English scientist Patrick Manson (1844–1922). The species name *ozzardi* goes back to Ozzard who discovered it. English: American connective tissue filarial.
2. **Geographic distribution/epidemiology**: Humid and warm regions exclusively in the New World focally from Mexico until North Argentina; several million infected persons (often not noted by infected persons).
3. **Biology, morphology**: The adult filariae reach as females a length of 8 cm and a width of 0.25 cm. The males are considerably smaller. Both live inside the peritoneal connective tissues and inside the pleural cavity of their hosts. The non-sheathed microfilaria measure 180–220 μm × 4–5 μm, thus are rather small and are found in the peripheral blood system all over the whole day and night in same amounts. **Vectors** are *Simulium* species besides midges of the genus *Culicoides*.
4. **Symptoms of the disease**: Symptoms are very low grade and severe cases were not yet reported.
5. **Diagnosis**: Giemsa colouring of microfilariae, which are present day and night inside the peripheral blood. In some regions up to 90 % of the humans are infected—very often undetected.
6. **Pathway of infection**: Percutaneously during bites of daytime-active *Simulium* and related species and of midges of the genus *Culicoides*, within which the microfilariae reach infectivity as larvae 3.
7. **Prophylaxis**: Avoidance of insect bites by use of repellents.
8. **Incubation period**: Due to low or (mostly) lack of clinical symptoms, infections remain mostly hidden.
9. **Prepatent period**: Weeks until months.

10. **Patency**: Years.
11. **Therapy**: Mostly not needed. **Ivermectin** (1 × 0.2 mg/kg bodyweight), **DEC** is not recommended due to high-grade side effects.

Further Reading

Adami YL et al (2014) New records of *Mansonella ozzardi*. Mem Inst Oswaldo Cruz Rio de Janeiro 109:87–92

4.4.20.3 *Mansonella streptocerca* (Mansonelliasis)

1. **Name**: The genus name honours the English scientist Charles Manson (1844–1922), while the species name is related to Greek: *streptos* = winded; *cercos* = tail. English: African skin filaria.
2. **Geographic distribution/epidemiology**: Nigeria, Ghana, Cameroon, Congo Basin. About several hundred thousand humans are constantly infected.
3. **Biology, morphology**: The adult, 27 × 0.08 cm sized females live in the subepithelial tissues of their hosts and depone there the 180–240 μm long, non-sheathed microfilariae, which stay inside the lymph systems of the subcutaneous tissues. **Vectors** are midges (*Culicoides* species), within which the infectious larva 3 is developed within 7–10 days. Then it may become transmitted during the next sucking act of the vector.
4. **Symptoms of the disease**: Itching and depigmentation of the skin; lymphadenopathy; especially inguinal adenopathies are common.
5. **Diagnosis**: Microscopically demonstration of the typical microfilariae by the help of so-called skin-snip probes (see *Onchocerca volvulus*).
6. **Pathway of infection**: Percutaneously during bites of *Culicoides* midges.
7. **Prophylaxis**: Avoidance of insect bites by the help of repellents.
8. **Incubation period**: About one year.
9. **Prepatent period**: About one year.
10. **Patency**: Years.
11. **Therapy**: Drug of choice against microfilariae is **diethylcarbamazine** (DEC, Hetrazan®). However, allergic reactions may be common (see *Loa loa*, Sect. 4.4.18).

Further Reading

Fischer P et al (1998) Detection of the filarial parasite *Mansonella streptocerca* in skin biopsies by a nested polymerase chain reaction-based assay. Am J Trop Med Hyg 58:816–20

Fischer P et al (1999) Long-term suppression of *Mansonella streptocerca* microfilariae after treatment with ivermectin. J Infect Dis 180: 1403–1405

4.4.21 *Dirofilaria* Species (Dirofilariasis)

4.4.21.1 *Dirofilaria immitis*

1. **Name**: Greek: *diro* = bristle. Latin: *filum* = filament; *immitis* = penetrating. English: Heart worm.
2. **Geographic distribution/epidemiology**: Worldwide in the tropics and subtropics. Dogs are commonly infected and represent the reservoir for human infections. Worldwide several hundred thousand of humans are infected; however, only a few are fully documented.
3. **Biology, morphology**: Main hosts of this filarial species are dogs and cats and only rather few humans are infected. The adult worms (females up to 30 cm long, males 18 cm long) were detected in the right chamber of the heart and inside the pulmonary arteries.
4. **Symptoms of the disease**: Unspecific heart problems besides heart hypertrophia, heart dilation and ascites.
5. **Diagnosis**: It is rather difficult to diagnose human dirofilariasis due to *D. immitis*, since only rarely (if at all) microfilariae are formed in humans. Infections of humans were mostly occasionally diagnosed by X-ray investigations, which showed the pre-adult worms in the different heart chambers. Circulating antibodies against *D. immitis* antigens are only hardly detected, since they occur only in very low amounts, so that ELISA results are often not convincing.
6. **Pathway of infection**: Percutaneously during bites of females of the mosquito genera *Aedes*, *Anopheles* and *Culex*, wherein the infectious larvae 3 are developed within 14 days after the blood meal.
7. **Prophylaxis**: Avoidance of bites by mosquitoes due to protection by the help of repellents. Furthermore, it is important to treat and to protect family dogs by application of products like Heartgard® in order to avoid their infection, which would be a possible source for human infections.
8. **Incubation period**: 3–9 months.
9. **Prepatent period**: 3–9 months.
10. **Patency**: 6–7 years (in dogs); in humans: unknown.
11. **Therapy**: Mostly not needed, since the diagnosis was mostly done when adult or pre-adult worms had been removed by the help of surgery. Treatment with **DEC** or **ivermectin** is possible (for dosage, see *Loa loa*; Sect. 4.4.18); however, it is dangerous due to important side effects.

Further Reading

Vollmer-Labarthe N et al (2015) Chemoprophylaxis of *Dirofilaria immitis* infection at a high challenge environment. Parasites Vectors 8:523

4.4.21.2 *Dirofilaria repens* (Skin filariasis)

1. **Name**: Greek: *diro* = bristl; *filarial* = filament-like; *repere* = creeping. English: Moving skin filariasis.
2. **Geographic distribution/epidemiology**: Worldwide, especially in the tropics and subtropics; hundred thousands of humans are infected.
3. **Biology, morphology**: Wandering larvae and pre-adults (8–20 cm × 0.4 mm) have been observed in the subcutaneous tissues of humans. Several specimens have also been detected in the eyes and were surgically removed. However, species determination was difficult and mostly impossible without the use of molecular biological methods. Therefore, it remained mostly unclear whether these stages belonged to *D. immitis*, *D. tenuis* or *D. repens*. However, since many animals around humans (dogs, cats, racoons, dogs, red foxes) may bear *D. repens*, humans should be infected, too. Especially recent PCR studies showed that up to 20 % of the dogs in some regions of Europe are infected and that autochthonous human infections occurred in these regions, too. **Vectors** are mosquitoes belonging to the genera *Aedes*, *Anopheles* and *Culex*.
4. **Symptoms of the disease**: Due to the growing worms, which remain in the swellings of the skin, inflammations had been observed accompanied by intense itching.
5. **Diagnosis**: Since microfilariae are practically absent inside humans, diagnosis is mainly based on specimens extracted surgically from the skin. Serodiagnosis is very unspecific.
6. **Pathway of infection**: Percutaneous transmission of larvae 3 during bites of mosquitoes of the genera *Aedes*, *Anopheles* and *Culex*.
7. **Prophylaxis**: Avoidance of insect bites by the help of application of repellents on the skin (Autan®, Viticks®).
8. **Incubation period**: Unknown
9. **Prepatent period**: None, since no larvae are produced.
10. **Patency**: Growing worm stages may survive for years in skin.
11. **Therapy**: Surgical removal of worm stages in the surface region of the skin.

Further Reading

Antolova D et al (2015) Case of human *Dirofilaria repens* infection manifested by cutaneous larva migrans syndrome. Parasitol Res 114(8):2969–2973

Hartwig V et al (2016) No evidence of *Dirofilaria repens* infection in red foxes (*Vulpes vulpes*) and racoon dogs (*Nyctereutes procyonoides*) from Brandenburg, Germany. Parasitol Res 115:867–871

Masny A et al (2016) Is molecular xenomonitoring of mosquitoes for *Dirofilaria repens* suitable for dirofilariosis surveillance in endemic regions? Parasitol Res 115:511–525

4.4.22 *Dracunculus medinensis* (Dracontiasis)

1. **Name**: Greek: *dracon* = dragon, snake. Latin: *medinensis* = originating from the Arabian town Medina. Arabian physicians removed this worm from human skin by the help of a wooden stick, which was split at the anterior end so that the worm could be taken and rolled on the stick during some following days without disruption of the worm. This aspect is very similar to the so-called **Aesculap** stick, which is surrounded by a snake and became a symbol for physicians of our days. English: Guinea worm (from Gulf of Guinea); Dragon worm. French: Fil d'Avicenna = Avicenna was a Persian physician (980–1037).
2. **Geographic distribution/epidemiology**: This worm is merely eradicated since even today in the smallest villages drinking water is no longer obtained from rivers but from wells. Thus, only a few thousands of humans are recorded to be infected in faraway regions in Africa, Arabia, Pakistan, India, Caribbean islands and Northern regions of South America. Besides *D. medinensis*, the species *D. insignis* and *D. lutrae* occur in animals. A WHO eradication program—Guinea worm eradication program (GWEP)—started in 2010.
3. **Biology, morphology**: The females of this worm are very long (50–-100 cm × 1–2 mm), while the males remain rather short (1–4 cm × 0.4 mm). In humans, they reach maturity in the subcutaneous tissues (mostly) of the legs and occasionally of the belly. Dogs become also infected. After copulation inside the uterus of the female, larvae (550–760 μm × 15–30 μm) hatch from the eggs and are released directly into the water, while the anterior end of the females breaks through the skin. This is rather easy, since the opening of the uterus is situated just 1 cm from the anterior end of the worm. The stimulus to do this is given when the skin is somewhat cooled down, e.g. in cases when people enter water, e.g., for fishing or getting water from lakes or rivers. In general, the females release several thousands of larvae at the same time in a milky appearing stream. These larvae survive for at least 4–7 days (at least 19 °C) and have to become ingested for further development by a small crustacean such as *Cyclops* (=water flea). Inside this intermediate hosts, the larva moults twice and thus reaches as larva 3 infectivity. Infections of humans but also of several animals occur, when drinking raw water containing such larvae 3. Inside the intestine of humans, the larvae 3 leave the intermediate hosts, penetrate the intestinal wall and enter inguinal and axial lymph nodes. After about 9–14 months, the worms reach their full length and sexual maturity. In general mostly only 2–5 worms are found in a patient (Fig. 4.64). In rare cases, up to 40 worms had been found in a person.
4. **Symptoms of the disease (Dracontiasis, dracunculosis)**: Typical specific symptoms are mostly lacking before the female appears for the first time in the centre of a popular skin protrusion of about 2–7 cm in diameter. In general, the skin is disrupted in the region between the knee and the knuckle. In the case of females, worm exits were also seen in the region below of the mammae. In bacterial superinfections, lymphangitis and sepsis may occur.

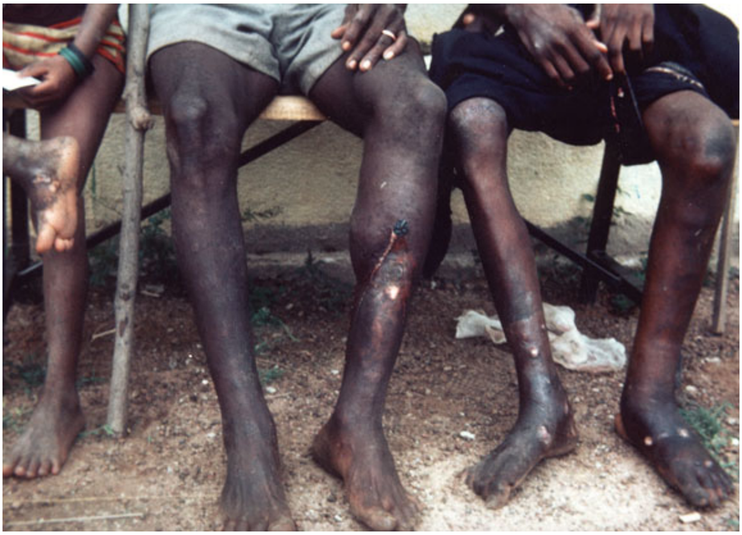

Fig. 4.64 Photo of the legs of three African patients showing portions of protruding female worms and thus derived skin alterations

5. **Diagnosis**: Observations of worms protruding from the centres of papulae of the leg skin. Calcified worms can be seen by the help of X-ray investigations.
6. **Pathway of infection**: Oral by drinking water containing small *Cyclops* crustaceans infected with larvae 3 of the worm. Since immunity is not developed, repeated infections may occur, thus increasing the worm load of a person.
7. **Prophylaxis**: Drinking water obtained from rivers or lakes in endemic regions should be cooked before drinking.
8. **Incubation period**: Symptoms of disease are due to secondary bacterial infections of the wound, which occurs at places where the anterior end of the worm breaks through the skin.
9. **Prepatent period**: 10–14 months (=this time is needed by the female to reach maturity and to become fertilized by males. Only then the female will break through the skin.
10. **Patency**: Several days up to a few weeks are needed to excrete all larvae; then the worms die, but their remnants stay inside the host, if they are not extracted by a physician or a natural healer while winding them up slowly on a stick.
11. **Therapy**: Since it was proven that excreted *Dracunculus* specimens were not provided with *Wolbachia* bacteria, antibiotic treatment is not helpful. Thus, the treatment of choice is still today the daily repeated slow extraction of further portions of the worm until the whole worm is removed. If the worm is disrupted during this process, the remnants will induce severe infections. If bacterial infections occur, immediate surgical removal of the remnants of the worm is needed.

Further Reading

Biswas G et al (2012) Dracunculiasis (Guinea worm disease): eradication without a drug or a vaccine. Philos Trans R Soc B 368:20120146

Eberhard MC et al (2014) The peculiar epidemiology of dracunculiasis in Chad. Am J Trop Med Hyg 90:61–70

Foster JM et al (2014) Absence of *Wolbachia* endobacteria in the human parasitic nematode *Dracunculus medinensis* and two related *Dracunculus* species infecting wild life. Parasites Vectors 7:140

4.4.23 Wandering Nematodes in Humans

This group contains nematodes, which do not reach maturity in humans, since they are not the specific final host. These migrating stages reach as larvae or pre-adult a length of several centimetres and induce—depending on the infested organ—different damages. The disease was described as so-called **creeping eruption**, since wandering swellings occur on the human skin. The following worms induce these symptoms:

1. Larvae of the so-called hookworms *Ancylostoma braziliense* and *Uncinaria stenocephala*—hookworms of dogs. The **infection** occurs by penetration of free larvae 3 into the skin of humans.
2. Larvae of the worm *Gnathostoma spinigerum*, which lives in Asia inside nodules inside the stomach mucosa of dogs and cats. These stages reach in humans a length of 2–9 mm and are characterized by an anterior spiny bulbous. The **infection** of humans occurs by ingestion of raw meat of birds and fish.
3. Larvae of roundworms of dogs, cats and racoons (e.g. *Toxocara canis*, *T. mystax*, *Baylisascaris procyonis*). The infection occurs by **ingestion** of larva-containing eggs.
4. Larvae of *Dirofilaria* species of dogs. The infection occurs by bites of vector insects of the genera *Anopheles* and *Culex*.

4.4.24 Microfilariae: Larvae of Filarial Nematodes

Microfilariae are the tiny larvae of a special group of the roundworms called filariae (Latin: fine filament/thread). They are transmitted during bites of the females of bloodsucking insects. The adult filarial live in contrast to many other groups of roundworm not in the interior of the intestine but in various tissues, from where their larvae may enter blood or lymph vessels. In general, the adults need a rather long time to reach maturity so that larvae mostly can be diagnosed only rather long after an infection. Thus, it is difficult to diagnose such an infection before the first microfilariae occur in the blood or in the lymph or in tissues.

Microfilariae appear in fresh preparations as intensively twisting, translucent, small worms (often in large numbers). A species diagnosis of these stages, which do not yet possess an intestine and measure—depending on the species—180–350 μm × 5–10 μm, is only possible after the use of concentration methods and staining. Both procedures, however, influence the size of these stages (e.g. formalin-fixed microfilariae appear 25 % larger than others dried by air or those fixed by methanol). The sizes listed below in the diagnostic keys must be considered under the above made limitations.

Diagnostic Key

(1a) Microfilariae are enclosed by a sheath (=enlarged egg shell)........................... **2**

(1b) Microfilariae are not enclosed by a sheath... **3**

(2a) The nucleus-free anterior region is mostly less long than its width, Nuclei occur in arrow loosely arranged behind each other; the worm tail is nucleus-free.. ***Wuchereria bancrofti*** (Figs. 4.59a, b)

(2b) The nucleus-free anterior region is longer than two times the width of the adult worm; the row of nuclei is dense, the terminal end shows two thickenings (each containing an nucleus)............................ ***Brugia malayi*** (Fig. 4.59c, d)

(2c) The nucleus-free anterior region is very short; the row of nuclei is dense, the row of nuclei reaches the terminal end of the microfilaria.................. ***Loa loa*** (Fig. 4.59f)

(3a) Tail of the microfilariae ends spiky and is free of nuclei........... ***Mansonella ozzardi***

(3b) The end of the tail of the microfilariae is rounded, one nucleus is situated there, so that a terminal button appears. ......***Mansonella perstans* (syn. *Dipetalonema*)**

4.4.25 Skin Mole (Creeping Eruption, Larva Migrans Cutanea)

The disease called creeping eruption is mainly based on migrating larvae of hookworms (Fig. 4.65a, b). However, also larvae of some tapeworms, cercariae of free trematodes (e.g. Schistosoma species) or the larvae of some fly species may induce similar symptoms. The hookworm larvae wander about 3–5 cm per day inside the skin by the help of excreted proteases, which digest the tissues. The pathways may become superinfected by bacteria. The wandering phase may take days up to several weeks until the immune system has killed these stages. Larvae of the intestinal nematode *Strongyloides stercoralis* may enter close to the outer side of the anus directly in the same host and thus initiate a so-called autoinfection. They also wander with a considerable high speed, so that they are described as “larva currens”. However, such an infection may disappear within 18 h, so that they are often no longer seen when arriving in the physician’s praxis. Besides those symptoms seen from outside, severe itching, erythemas and a high eosinophilia

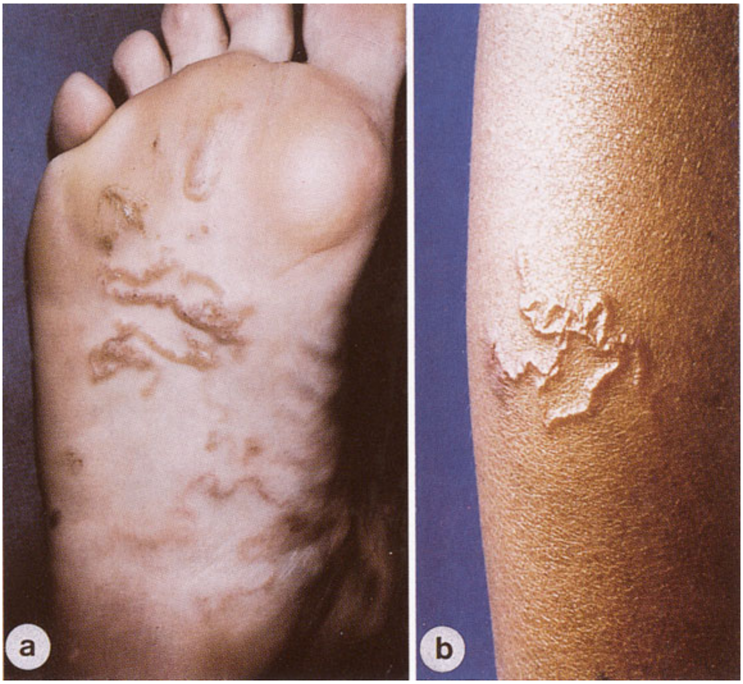

Fig. 4.65 Photos of the foot sole (**a**) and the arm (**b**) of patients showing wandering larvae of nematodes (=creeping eruptions)

may occur. Methods of prophylaxis are to avoid contacts with untreated dogs and cats, to clean animal cages by use of hot water from fecal remnants and to deworm house animals at regular intervals.

As means for therapy of infections by larva migrans cutanea, it is recommended to spray ethyl chloride onto affected skin region or to kill the larvae by local application of a lotion containing at least 15 % tiabendazole. The application of albendazole or mebendazole must be done for at least 10–15 days, while in the case of ivermectin mostly a single dose is sufficient. In the case of massive infection, an additional treatment with antihistamines is needed in order to avoid anaphylactic reactions.

4.4.26 *Thelazia* Species (Thelaziasis)

1. **Name**: The name was given to honour the discoverer of these worms (Dr. Thelaz). English: Eyeworm.
2. **Geographic distribution/epidemiology**: Worldwide, e.g. in Germany are up to 15 % of cattle, 25 % of horses and about 5 % of dogs infected. Also many cases of human infections were diagnosed.

3. **Biology, morphology**: The larvae of the different species (e.g. cattle: *T. skrjabini*; horse: *T. lacrymalis*; dogs/cats: *T. callipaeda*), which are transmitted by flies onto the eyes of the hosts, enter the conjunctival region, where they reach maturity. They appear whitish and reach a species specific length of 0.5–2 cm. The eggs are laid into the fluid of the conjunctival sack where the larvae hatch from the thin-shelled eggs and develop into the larva 3 within 4 weeks and are ready to become transported to further hosts. Besides the above-cited species also birds may become infected as well as accidentally humans.
4. **Symptoms of the disease**: In cases of a few worm larvae, only low-grade symptoms occur. In cases of more than 10 larvae, eye symptoms like conjunctivitis, intense production of tears and high light sensitivity or even keratitis besides bacterial superinfections may occur. In the case of human infections, keratitis is the most common symptom.
5. **Diagnosis**: Rinsing the conjunctival sack and microscopical examination of the centrifuged material shows potentially present larvae 1 which measure about 200 μm in length.
6. **Pathway of infection**: Eye contacts with flies.
7. **Prophylaxis**: Fly control in human dwellings.
8. **Incubation period**: Days until weeks.
9. **Prepatent period**: 3–6 weeks.
10. **Patency**: About 1 year, if not new infections occur.
11. **Therapy**: Rinsing of the conjunctival sack; surgical removal of adult worms; chemotherapy with avermectins.

Further Reading

Hodzic A et al (2014) The spread of zoonotic *Thelazia callipaeda* in the Balkan area. Parasites Vectors 7:352

Motta B et al (2012) Therapeutic efficacy of milbemycin oxime/praziquantel oral formulation (Milbemax®) against *Thelazia callipaeda* in naturally infected dogs and cats. Parasites Vectors 5:85

Van DN et al (2012) The first human case of *T. callipaeda* infection in Vietnam. Korean J Parasitol 50:221–223

4.5 Worms Belonging to Further Animal Phyla

4.5.1 Pentastomida (Pentastomiasis)

This group (Pentastomida, Linguatulida) is peculiar, since it has developed several morphological convergences with many other animal phyla. However, a clear relationship has never been seriously proven. The most recent classification as member of the Crustaceans, which is based on the finding that their body is apparently divided into an anterior cephalothorax and a terminal abdomen, is not yet completely accepted. The appearance and structure of their cuticle (Fig. 4.66a, b) is most similar to that of the insects, since it contains much more chitin than nematodes and crustaceans.

1. **Name**: Greek: *penta* = five; *stoma* = mouth. This name is based on the erroneous observation of 5 mouth openings, while only one exists. The observed "other four" are just surface protrusions. Linguatulids is another name for this peculiar group. The species name *Linguatula serrata* has its origin in Latin: *lingua* = tongue; *serrare* = disrupting. English names for this group are pentastomids and linguatulids.
2. **Geographic distribution/epidemiology**: *Linguatula serrata*: worldwide; species of the genera *Armillifer* and *Porocephala* are found in Asia and Africa. Final hosts of species belonging to the three genera are snakes in Africa (*Armillifer*), snakes in Asia (*Porocephalus*) and dogs, foxes, wolves and occasionally humans in *Linguatula* species. The documented human cases are rare and apparently involve only persons with common contacts to snakes. However, it is suspected that much more human cases are hidden.
3. **Biology, morphology**: The adult males and females of the genera *Armillifer*, *Porocephalus* and *Linguatula* live inside the cavities of nose, throat and lungs of meat-ingesting vertebrates (Fig. 4.66a, b). In the case of *Linguatula serrata*, the females may reach a size of up to 13 cm in length, while the males are considerably smaller (~2 cm). They are mainly found in dogs, but are occasionally also seen in humans. *Armillifer* species (Fig. 4.66a, b) reach similar

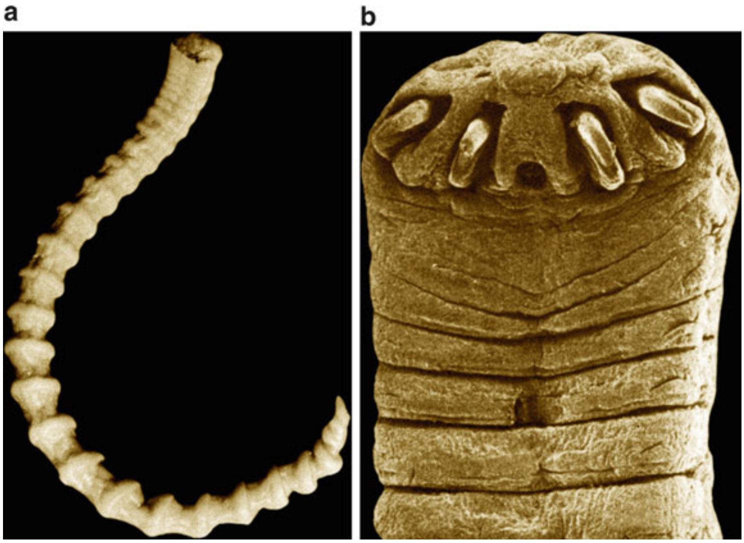

Fig. 4.66 Light (**a**) and scanning (**b**) electron micrographs of a total worm of *Armillifer armillatus* (**a**) and its anterior pole (**b**)

sizes like *Linguatula serrata*, while *Porocephalus* species measure 7 cm at the maximum. The eggs of *L. serrata* measure 60 × 90 µm, while those of *Armillifer* reach a length of 110 µm. All eggs are excreted within the nasal slime and contain already the larva 1. If such eggs are ingested by plant-eating vertebrates (inclusive humans), the hatched larvae penetrate the intestinal wall and are transported by blood into different organs such as muscles, liver and lungs, where they grow up via several moults. *L. serrata* reaches there a size of 4–5 mm; *A. armillatus* 2–3 mm. If the meat of these plant-feeding intermediate hosts is ingested by carnivorous animals (and humans), the small larvae reach maturity inside the nasal cavities and/or in the anterior tracheal or intestinal tractus. The females are able to produce up to 500,000 eggs per day (**!**).

4. **Symptoms of the disease**: Depending whether humans are infected as intermediate or final hosts, different symptoms may occur:
   (a) In the case of humans serving as **final hosts** for *L. serrata*, the so-called **Halzoun syndrome** may occur. In this case, air pathways in the nose may become completely blocked leading to oedemas in the face and often deafness. In cases of strong sneezing, worms may become suddenly expelled.
   (b) In the case of humans serving as **intermediate hosts,** their inner organs may be infected by (often) rather large numbers of larvae. This may—depending of the affected organ—lead to death if numerous parasites are present. Death due to such larval stages was relatively often seen in Africa, when *post-mortem* inspections had been done.
5. **Diagnosis**: Microscopic observation of eggs inside nasal slime or by accidental occurrence of *L. serrata* stages after sneezing. Histological preparations of organs or X-ray examinations may show active or dead worm stages—however, these are mostly accidently findings.
6. **Pathway of infection**: The infection of humans may occur on different ways:
   (a) Humans ingest worm eggs on salad or plants. The hatching larvae are spread in the body and enter different organs. This pathway is especially important in Asia and Africa, since there are snakes, which live close to humans, common final hosts of worms of the genera *Armillifer* and *Porocephalus*.
   (b) Humans ingest raw or undercooked meat of infected intermediate hosts. In the case of *L. serrata*, the ingested larvae may reach maturity inside the nose or mouth region.
7. **Prophylaxis**: Avoidance of direct contacts to feces of dogs and snakes in endemic regions. Intense washing of potentially contaminated plants and eating exclusively well done meat. House dogs should be educated not to feed rodents.
8. **Incubation period**: Depending on the status of the ingested infectious material, different periods are needed until first symptoms occur:
   - In the case that larvae-containing raw meat is ingested, pre-adult stages may lead to first symptoms in the oropharyngeal system already after a few days past infection.

   - In the case of the oral uptake of eggs from infected snakes, it may take 6–7 months until first symptoms occur due to wandering larvae in the human body.
9. **Prepatent period**: 6–7 months in the case of *L. serrata*.
10. **Patency**: 15 months in the case of *L. serrata*, rarely longer.
11. **Therapy**: Provocation of sneezing may lead to excretion of worms from nasal regions; surgical removal of worms from the nasal-tracheal tractus (Fig. 4.67).

Further Reading

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Chen SH et al (2010) Multi-host model based identification of *Armillifer agkistrodontis* (Pentastomida): a new zoonotic parasite from China. PLoS Negl Trop Dis 4(4):e647

Gjerde B (2013) Phylogenetic position of *Linguatula arctica* and *L. serrata*. Parasitol Res 112:3517–3525

Kelehear C et al (2011) Using combined morphological, allometric and molecular approaches to identify species of the genus *Raillietiella* (Pentastomida). PLoS One 6(9):e24936

Tropeninstitut Hamburg (2013) *Armillifer armillatus*: pentastomiasis in an African immigrant in Germany. Emerg Infect Dis 19:507–510

4.5.2 *Macracanthorhynchus hirudinaceus* (Acanthocephaliasis)

Acanthorhynchidae were kept for long as special subphylum of the nematode, but later after the discovery of peculiar morphological, physiological and phylogenetic differences, it became an own separate phylum.

The members of the different classes of the always heterosexual and parasitic members of the Acanthocephala, which reach a length of up to 70 cm, are characterized by their cylindric unsegmented outer aspect and by their protrusible, hook-armed proboscis (Figs. 4.68 and 4.69). They do not possess an intestine, but take up their food via their outer tegument, which, however, is considerably thicker than that of the cestodes (tapeworms). Recently, other acanthocephalan worms besides *M. hirudinaceus* were found to infect humans, too (e.g. *Bolbosoma capitalum*, *Pomphorhynchus rhynchus* spp.)

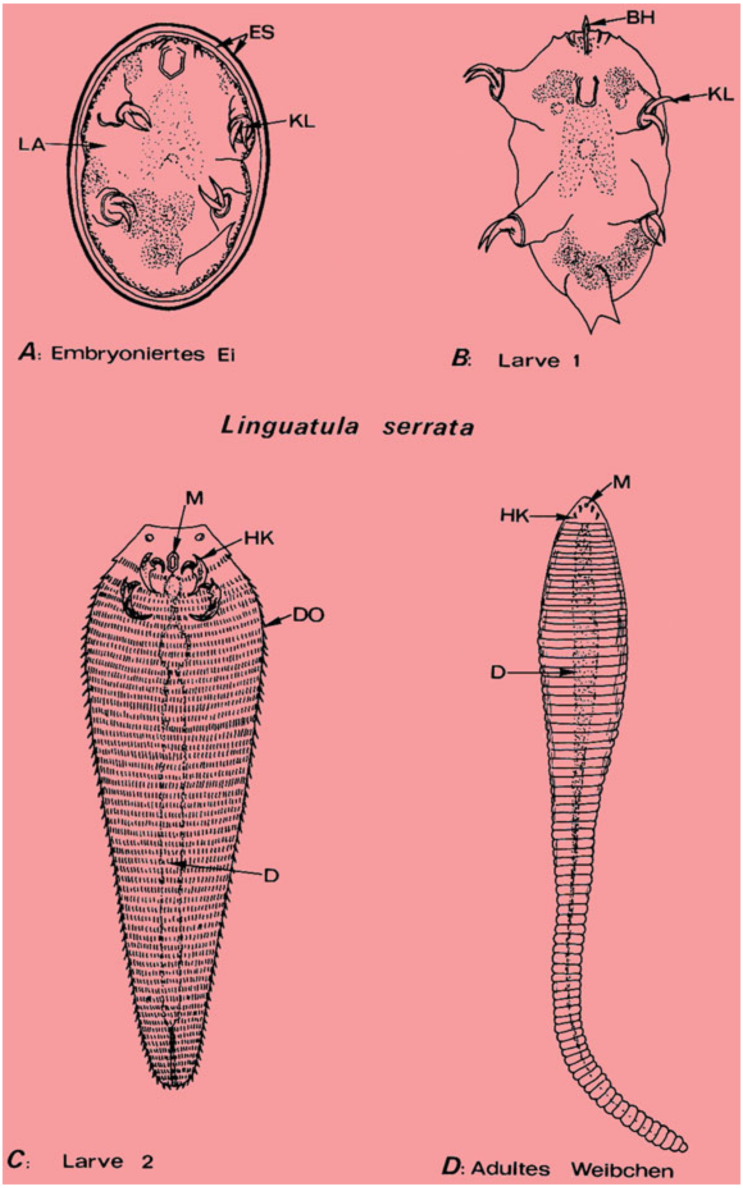
ES
LA
KL
A: Embryoniertes Ei
BH
KL
B: Larve 1
Linguatula serrata
M
HK
DO
D
C: Larve 2
M
HK
D
D: Adultes Weibchen

Fig. 4.67 Diagrammatic representations of the developmental stages of the pentastomid worm *Linguatula serrata*. (**a**) Embryonated egg; (**b**) Larva 1; (**c**) Larva 2; (**d**) Adult female. *BH* bore hook, *D* intestine, *DO* thorn, *ES* egg shells, *HK* hook, *KL* claws at the legs, *LA* larva, *M* mouth

System
Phylum: Acanthocephala
1. Class: Archiacanthocephala
Order: Moniliformida
Genus: *Moniliformis*
Order: Oligacanthorhynchida
Genus: *Macracanthorhynchus*
Genus: *Prosthenorchis*
2. Class: Palaeacanthocephala
Order: Echinorhynchida
Genus: *Acanthocephalus*
Genus: *Echinorhynchus*
Genus: *Pomphorhynchus*
Order: Polymorphida
Genus: *Polymorphus*
Genus: *Filicollis*
3. Class: Eocanthocephala
Order: Neoechinorhynchida
Genus: *Neoechinorhynchus*
Genus: *Paratenuisentis*

1. **Name**: Greek: *makros* = large, great; *acantha* = with spines, spikes; *rhynchos* = snout. Latin: *hirudinaceus* = leech-like. English: thorny headed worm; giant thorny worm
2. **Geographic distribution/epidemiology**: Worldwide, in regions with rearing pigs at free run, especially in China and Indonesia and in general in regions, where humans eat beetles. Several hundred thousands of humans are infected in these regions.
3. **Biology, morphology**: This species, which is also called thorny pig worm or giant *Acanthorhynchus*, has heterosexual adults, which are characterized by protrudable anterior bulbous, which bears numerous hooks (Figs. 4.68 and 4.69), which are used to anchor the intestine-less worm at the intestinal mucosa. In the intestine of the pig, the worms reach maturity and a length of 70 cm in the case of females but only 15 cm as males. Inside humans the females never reach full sexual maturity, so that eggs cannot be found in human feces. Pigs, however, excrete full infectious eggs, containing the so-called **acanthor larva**. The eggs measure about 70–110 μm × 40–65 μm and have to be ingested by beetles or their larvae. About 60 beetle species are known as vectors, within which via an **acanthella larva** finally the infectious **cystacanth larva** is produced. If pigs ingest such larvae within beetles, the adult worms become developed within 8–12 weeks. In humans, however, the worms do not reach maturity but also a considerable length.
4. **Symptoms of the disease**: The juvenile worms become anchored by their strong hooks at the mucosa of the intestine and are able (especially in children)

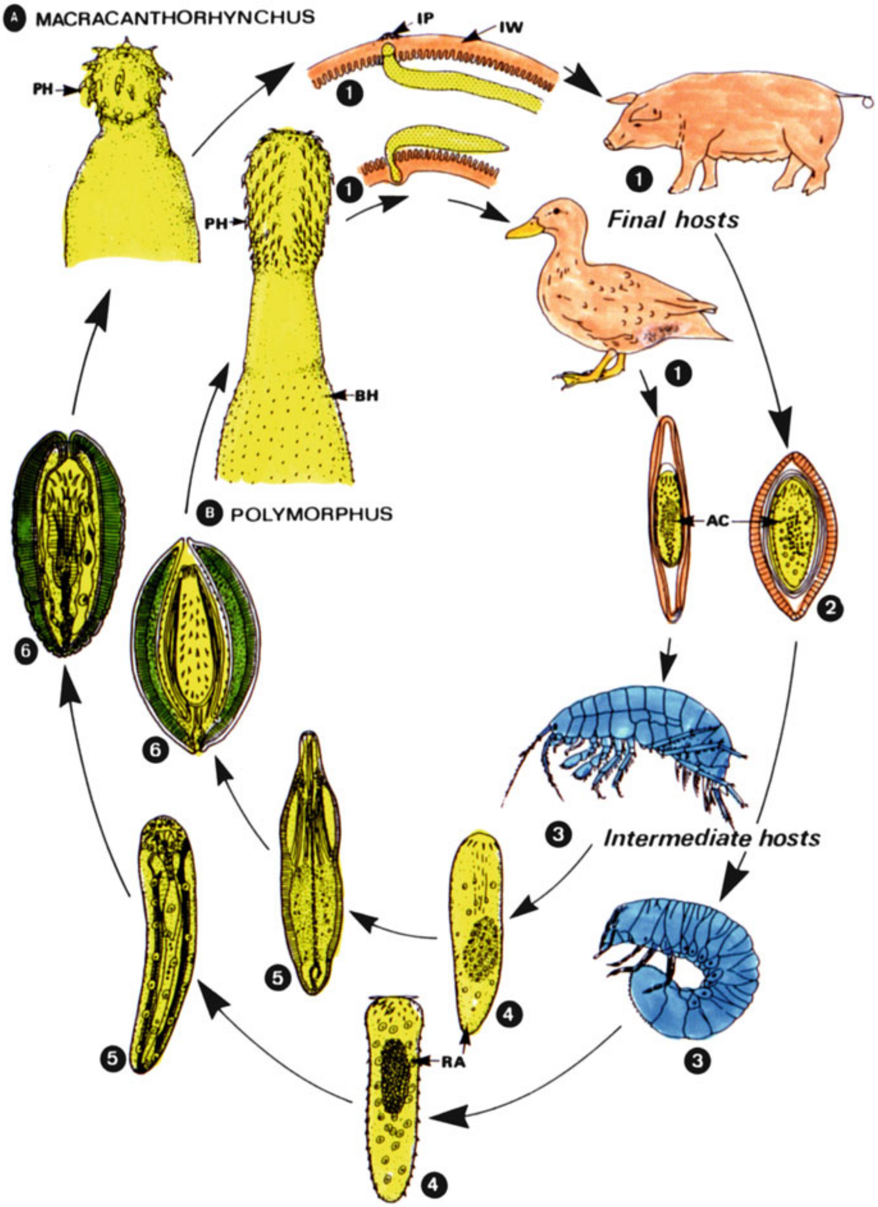
A MACRACANTHORHYNCHUS
PH
IP
IW
1
1
1
PH
Final hosts
1
BH
B POLYMORPHUS
AC
2
6
6
3
Intermediate hosts
5
4
3
RA
5
4

Fig. 4.68 Diagrammatic representation of the life cycle of two species of acanthocephalans (*Macracanthorhynchus hirudinaceus, Polymorphus minutus*). (**1**) Worms in final hosts (humans may replace pigs). (**2**) Eggs containing the acanthor larva. (**3**) Intermediate hosts (water crustaceans or larval or adult beetles). (**4**–**6**) Larvae: acanthor, (**4**) acanthella (**5**), cystacanth (**6**). *AC* acanthor, *BH* hook at the body, *IP* inflamed region, *IW* intestinal wall, *PH* hooks of the proboscis (=anterior protrusion), *RA* hatched acanthor

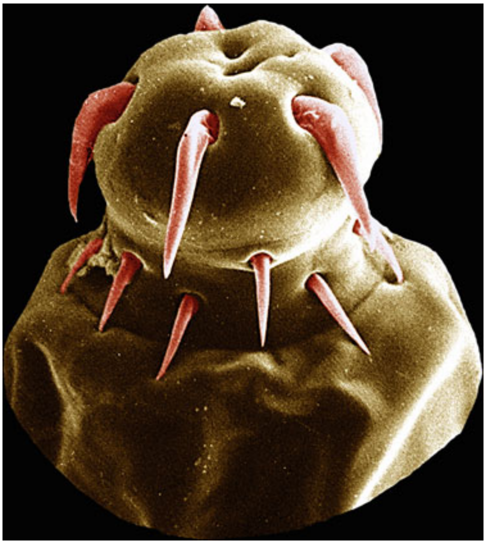

Fig. 4.69 Scanning electron micrograph of the anterior end of an acanthocephalan

to perforate the intestinal wall. Thus, in some regions of China surgery due to intestinal symptoms such as acute abdomen or peritonitis after acanthocephalan infections are much more common than these due to appendix inflammations.

5. **Diagnosis**: Since during human infections no eggs are excreted within the feces, X-ray investigations after ingestion of contrast-compounds are most successful. Serological investigations are much less useful, if available at all.
6. **Pathway of infection**: Oral by uptake of larvae-containing beetles or portions of them. Therefore, children are endangered, when playing with beetles or people in several regions of China where beetles are eaten raw.
7. **Prophylaxis**: Avoid contacts to beetles in pig-rich rural regions.
8. **Incubation period**: 2–12 weeks.
9. **Prepatent period**: In the case of pigs: 8–12 weeks; in the case of humans, no eggs are produced.
10. **Patency**: Months, until the human body has killed the worms, which are eventually enclosed in granules.
11. **Therapy**: In the case of pigs, a dosage of 1.0–1.5 mg loperamid (e.g. Imodium® per kg/bodyweight two times daily on three consecutive days was successful), added by a certain amount of ricinus oil. For humans, the same application should be successful.

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4.5.3 Leeches (Annelida)

This group of worms received its name due to their homonymous segments. They are inside and outside clearly differentiated from other worms such as the roundworms (Nematodes) and flatworms (Cestodes, Trematodes). However, most of the mostly dioecius annelids are free living and only a few (especially in the group of the Hirudinea) had become parasites.

Hirudo medicinalis and Relatives (Blood Sucking Medical Leech)

1. **Name**: Latin: *hirudo* = leech; *medicinalis* = relation to medicine.

System (shortened)
Phylum: ANNELIDA
Class: Polychaeta (with many bristles, free living)
Class: Myzostomida (parasites on crinoids)
Class: Clitellata (worms with a clitellum)
Order: Oligochaeta (with a few bristles, mostly free living)
Order: Hirudinea (leeches, many parasites)
Family: Rhynchobdellidae
Family: Pharyngobdellidae
Family: Gnathobdellidae (with jaws)
Family: Acanthobdellidae

2. **Geographic distribution/epidemiology**: *Hirudo medicinalis*: in Europe, North Africa, Asia, North America; related species worldwide. In the jungles of Ceylon and South East Asia, leeches of the family Haemadipsidae stay on plants and attack from there humans and animals.
3. **Biology, morphology**: *Hirudo medicinalis* and the South-European/Turkish *Hirudo* species belong to the phylum Annelida. Similar species are found practically worldwide living in lakes and in other watery biotopes luring for hosts. On its dorsal side, *H. medicinalis* is characterized by its olive-greenish colour and by six longitudinal brownish stripes. The length is about 15 cm, but these leeches are very flexible. The diameter reaches (unfed) about 1.5 cm. When reaching sexual maturity, this leech develops the so-called **clitellum** at the 26–40th segment, which excretes slime within which the eggs are collected and (after its drying transformation to a cocoon) are set free. The young leeches do not suck blood and live as predators, while elder ones start to suck blood at a broad spectrum of hosts entering their watery biotope. Host finding occurs by registration of the concentric waves produced by a host and by the help of chemoreceptors and their five pairs of relatively simple eyes. After being attached at a host, its skin is cut by the help of three incisive, blade-like teeth, at the top of which the exits of single salivary glands release substances which reduce pain, enlarge blood vessels and stop blood coagulation. Especially the so-called **hirudin** (an anticoagulant) keeps the blood fluid, so that the leech is not disturbed during feeding. While adult leeches suck about 10–15 ml blood during one blood meal, further 50 ml blood may be lost due to the ongoing bleeding of the wound after the detachment of the worm. Leeches may starve one or up to two years. Further important Gnathodellidae (leeches with jaws) are:

In **Africa** and **Asia**: *Macrobdella* species and *Limatis* species (e.g. *Limnatis nilotica* is 8–12 cm long and attacks animals and humans. During swimming, these leeches may enter the nasal cavities of humans and animals and can only hardly be removed. Smaller examples of these species also had been found in the human vagina and bladder. In **India,** the leech *Hirudinaria granulosa* is used (as formerly *H. medicinalis* in Europe) as a medical device. In **South and Central America,** the jawless species *Haementaria officinalis* is used for similar activities as *Hirudo medicinalis*.

Attention: All these leeches may be vectors of viruses, bacteria and parasites, which they might have ingested from humans at a preceding blood meal (Nehili et al. 1994). Thus, for such purposes only leeches should be used after rearing in agent-of-disease-free cultures (Figs. 4.70 and 4.71).

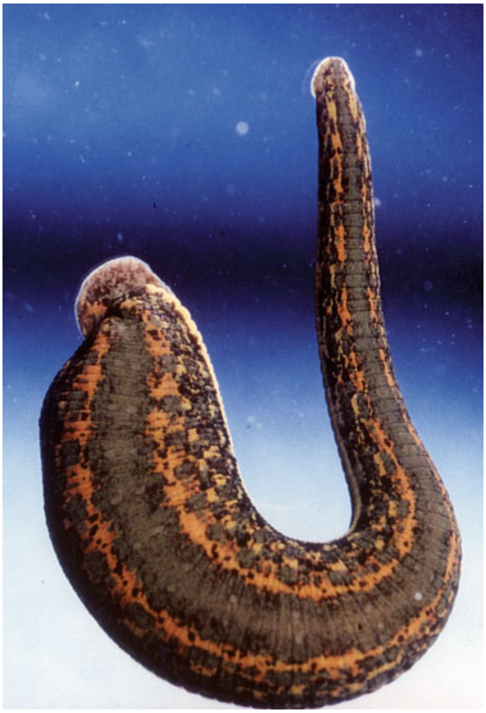

Fig. 4.70 Macrophoto of the dorsal side of an adult *Hirudo verbena* leech

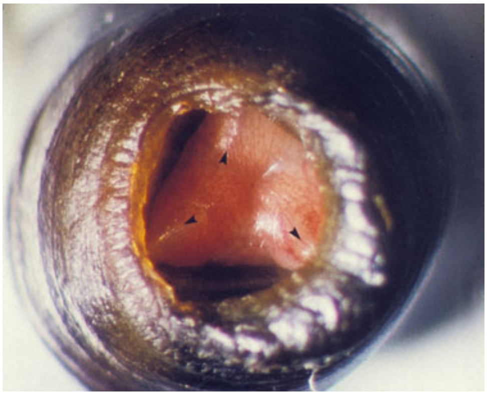

Fig. 4.71 Macrophoto of the three cutting teeth of a *Hirudo medicinalis* leech

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4.6 Available Compounds, Methods and Means to Control Protozoan and Helminthic Parasites

1. **Introduction**

   Parasites in a strict sense belong to the animal phylum groups of

   - Protozoa
   - Metazoa with its subgroups of
     - Myxosporea
     - Platyhelminthes
       Trematodes (Mono-, Digenea = flukes)
       Cestodes (tapeworms)
     - Nemathelminthes (roundworms)
     - Acanthocephala (thorny headed worms)
     - Annelida (sic leeches)
     - Pentastomida (tongue worms)
     - Arachnida (mites, ticks)
     - Insecta (insects)
     - Crustacea (crustaceans)

   The members of the animal group of parasites have developed highly sophisticated methods to enter potential hosts (humans, animals), to survive inside their hosts and to give rise to offspring, which is able to survive outside the host. Thus, a successful elimination of infections by parasites needs sophisticated strategies that comprise a broad spectrum of measurements. The following approaches are needed:

   - Development of broad spectrum and specialized diagnostic methods
   - Development of medicaments to treat internal parasitosis
   - Development of acaricides and insecticides
   - Development of repellent compounds, which prevent skin penetration
   - Development of immunological protection by vaccines
   - Development of methods and tools of cleaning, sterilization and disinfection of working places, equipment, dwellings, hospitals, stables, etc.
   - Development of prophylactic protection from infections by establishment of hygienic standards and their constant control and amelioration as well

as in stables, in dwellings and in surroundings of humans and farmed animals

- Development of methods of elimination of human and animal feces
- Development of methods to avoid entrance of particles of human and animal feces in lakes, rivers and drinking and bathing water
- Development of urgency plans to minimize consequences in case one of the described targets had been missed

2. **Available medications against parasites (selected compounds)**

2.1 **Chemical compounds**

2.1.1 **Antiprotozoal compounds and target genera**

- Albendazol (*Giardia*, *Echinococcus* species)
- Allopurinol (*Leishmania* species)
- Amphothericin (*Acanthamoeba*, *Naegleria*)
- Chloroquine (*Plasmodium vivax*)
- Clindamycine (*Toxoplasma gondii*, *Neospora*, *Babesia*)
- Cotrimoxazole (*Isospora belli*, *Cyclospora cayetanensis*, *Encephalitozoon* sp.)
- Doxycycline (*Plasmodium* species)
- Diclazuril (Coccidia)
- Eflornithin (*Trypanosoma* species)
- Emodepsid + Toltrazuril (*Isospora*)
- Fenbendazole (*Giardia*, *Encephalitozoon*)
- Furazolidon (*Giardia*)
- Halofuginone (Coccidia, *Theileria* species)
- Imidocarb (*Babesia* species, *Hepatozoon* species)
- Lasalocid (Coccidia)
- Manduramycin (Coccidia)
- Mefloquin (*Plasmodium* species)
- Meglumantimonat (*Leishmania donovani*)
- Metronidazole (*Giardia*, *Blastocystis*, *Trichomonas vaginalis*)
- Miltefosin (*Leishmania* species)
- Monensin (Coccidia)
- Narasin (Coccidia)
- Nifurtimox (*Trypanosoma cruzi*)
- Nitroimidazole (*Balantidium coli*, *Entamoeba histolytica*)
- Pyrimethamine + Sulfonamides (*Toxoplasma gondii*)
- Pyrimethamine (*Toxoplasma gondii*)
- Robenidine (*Eimeria* species)
- Salinomycin (Coccidia)
- Semduramycin (Coccidian)
- Sodium stibogluconate (*Leishmania donovani*, *Leishmania* species)
- Spiramycin (*Toxoplasma gondii*)
- Sulfadiazin (*Toxoplasma gondii*)

- Suramin (*Trypanosoma cruzi*)
- Toltrazuril (*Eimeria* species)

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Arthropods

5

Name: Greek: *arthron* = segment; *pus, podos* = foot.

The **metameric arthropods** are named with respect to their segmented legs (Acarina, mites) which probably derive from locomotory appendages similar to the parapodia of recent polychaetes. The **chitin-protein exoskeleton** is common to all groups of arthropods, is secreted by chitogeneous cells of the epidermis (**hypodermis**) beneath it and covers not only the external surface but also passes through the mouth into the anterior part of the intestine (stomodaeum). The rectal part of the alimentary system is called proctodaeum. The exoskeleton in the form of chitinous single plates is connected by fine membranous elements, thus allowing movements and body flexing by means of the strong inner muscular systems and the hydrostatic pressure of the body fluid. A non-changeable chitinous cover would hinder growth of the arthropods; thus, it is cast off periodically and a new larger exoskeleton is formed during **moult** (**ecdysis**). Most arthropods are monoecious; copulation and internal fertilization are characteristic in the majority of species. **Ontogenesis** proceeds in all parasitic forms as **metamorphosis** involving at least one and sometimes several larval (nymphal) stages. The circulatory system is open with a primitive dorsal heart; respiratory systems of various kinds (gills, tracheae, lungs, etc.) may occur, as well as different forms of the excretory tract (Malpighian tubules, coxal and antennal glands, etc.).

The structure of the intestine and its appendages varies considerably among the various arthropod taxa, depending on their different ways of living and feeding. Even when they feed in the same way (e.g. blood-sucking), different (though convergent) structures, methods and strategies have been developed in insects, mites and ticks.

Arthropods have traditionally been divided into two subphyla. Those with antennae have been placed within the subphylum **Mandibulata**, thus named because the first postoral appendages are mandibles. Those that lack antennae and mandibles are commonly placed in the subphylum **Amandibulata** (others prefer the term **Chelicerata**, thus named because the first postoral appendages become feeding organs called chelicerae).

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System (Overview)

Recent classifications of the arthropods are under discussion (especially the rank of different taxonomic groups). However, the following groups are accepted in toto:

Phylum ARTHROPODA
Subphylum: Trilobitomorpha (the fossil trilobites)
Subphylum: Chelicerata
Class: Merostoma (horseshoe crabs and fossil eryperids).
Class: Arachnida (including orders Araneae = spiders, scorpions, Acarina, ticks, mites, etc.).
Class: Pycnogonida (=Pantopoda, sea spiders).
Subphylum: Tracheata
Class: Chilopoda.
Class: Progoneata.
Class: Insecta (Hexapoda).
Subphylum: Diantennata (Branchiata)
Class: Crustacea.

5.1 Scorpions

1. **Name**: Greek: *scorpios* = scorpion, the biting one.
2. **Geographic distribution/epidemiology**: Scorpions are rather large arthropods, which are characterized by segmented legs (4 pairs). Especially characteristic are the large pedipalps, which are provided with typical scissor-like terminal attachment systems (Fig. 5.1a, b) and a large number of fine hair, which help to detect their prey animals. The scorpions possess two median eyes, and depending on the species 2–5 pairs of laterally situated ones. The prey is cut into edible pieces by the help of the anteriorly positioned pair of so-called cheliceres (Greek: *chele* = scissors, claw; *keras* = horn). In contrast to spiders, the cheliceres are not connected to venomous glands. The body of the scorpions consists of the so-called **prosoma**, which consists of six segments bearing ventrally the four legs, a **mesosoma** and a posterior tail-like region (**metasoma**) consisting of seven segments. The tail-like terminal end of the metasoma is equipped with the sting of a poison producing system. This poison is used to kill the prey which is kept at the anterior side by the help of the two claws (cheliceres). At the ventral side (sternal region), the scorpions are equipped with a pair of so-called combs which are covered by numerous sense organs, which are used (among others) during copulation of two partners. Scorpions are nightly active and are hidden during daytime, so that contact to humans mostly occurs unwillingly during accidental contacts.
3. **Effects of scorpion bites**: The reactions of humans on scorpion bites may be completely different and depends neither on the size of the scorpion nor on the

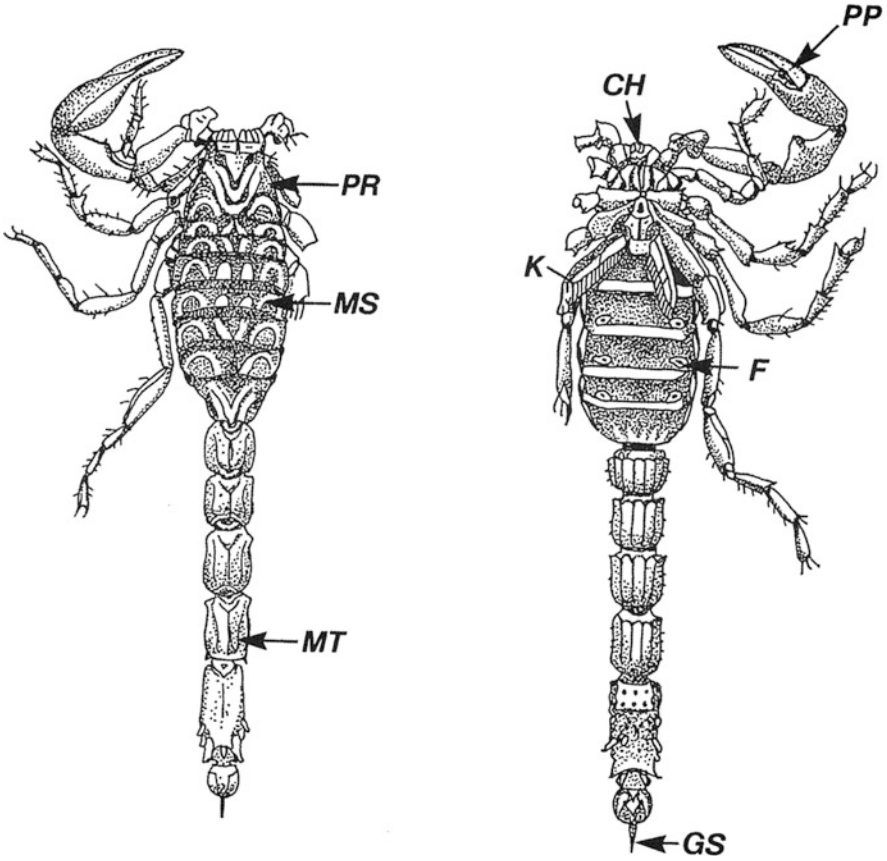

Fig. 5.1 Diagrammatic representation of both sides of a scorpion. *CH* cheliceres; *F* lung; *GS* sting of poisonous gland; *K* combs with sense organ; *MS* mesosoma; *MT* metasoma; *PP* pedipalps (as scissors); *PR* praesoma

amount of poison injected, but mainly on the type and composition of the poisonous substances. There are two different types of poison described:

(1) A locally acting type of poison, which may be dangerous only for very sensitive persons.

(2) The second type acts as a neurotoxin, which may lead to death (especially often in children).

Bites of many scorpion species show no or only low-grade effects in humans (e.g. the South European species *Euscorpius italicus*, *E. carpathicus*) are practically non-poisonous. However, the situation is different for *Buthus occitanus*. In Southern Europe, the specimens of this brownish, about 1.5–7 cm long scorpion are not poisonous, while they are extremely poisonous in North Africa and Eurasia. Their bite is very painful and pain persists for many hours. Fever and strong headache may last for up to 2 days.

Further members of the family Buthidae occur worldwide and may lead to life-threatening symptoms. In cases where humans are attacked, the following symptoms are common:

(1) The biting site is inflamed, appears reddish and is swollen.
(2) Fever starts suddenly.
(3) Sudden intense sweating occurs.
(4) Increase of saliva production.
(5) Muscular spasms are caused.
(6) Sight defects occur suddenly.
(7) Dizziness leads to immobility.
(8) Breathing problems occur.
(9) Paresis is spreading over both legs.
(10) Death may occur.

The intensity of symptoms, however, always depends on the amount of injected poison.

Especially dangerous are the following species:

- ***Androctonus australis***

  This species occurs in Northern Africa (in the Atlas Mountains and in the Sahara): the poison is as strong as that of a cobra snake and kills a dog within 7 min.
- ***Leiurus quinquestriatus***

  This species occurs in Eurasia regions.
- ***Centruroides* species (e.g. *C. exilicauda*)**

  These species are especially common in southern states of the USA and in Mexico. They led in Arizona during the years 1929–1948 to two times more human death cases than all other poisonous animals together.

4. **Therapy**: The best results of a treatment of scorpion bites are obtained by use of so-called antisera, which in general are available in regions with numerous scorpions. Treatment must be done as short as possible after a bite. If this is not possible, the affected leg/arm should be covered by a compress in order to minimize the transportation of the poison within the blood to other organs (brain, heart). The compress, however, should be loosened after 30 min for about 10 min. The biting site should be immersed into icy water. The quickest transportation to a serum station is most important. Sucking off poison by mouth is extremely dangerous, since the poison may enter the body via small wounds inside the mouth cavity.

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5.2 Spiders (Arachnida)

1. **Name**: Greek: *Arachne* = spider; *arachnion* = spider net.
2. **Geographic distribution/epidemiology**: Spiders, which may live hidden inside human dwellings, in stables, but occur mostly in the nature luring for their targets, which mainly comprise arthropods and only in a few species small mammals. People's opinion on spiders is bad, since their poison and aggressiveness are highly overestimated. The body of the spider consists of two large regions. The anterior **prosoma** is provided with four pairs of walking legs, the two biting mouthparts (**cheliceres**) and two **pedipalps** (Figs. 5.2, 5.3). The posterior body (**opisthosoma**), which in general is much larger than the prosoma, is connected by a very tiny, motile stalk-like segment with the anterior body region, but it is not provided with extremities. At the terminal end of the opisthosoma, there are situated the anus and in some species the spinning warts, which originate from limb buds. The sexual opening is situated in the midst of the body (=in the eighth segment just at the anterior end of the opisthosoma). The female spider excretes—after a copulation—eggs, which give rise to tiny spiders, which look like adults and grow up to full size while proceeding several moults.
3. **Effects of bites**: Humans are only accidental targets of spider bites. In most spider species, the mouthparts (cheliceres) are unable to perforate the elastic human skin. There exist many fairy tales on spider bites. For example, it was believed for long (starting in the Medieval) that humans—if bitten by the South European spider *Lycosa tarantula*—would start an ecstatic dance (*tarantella*). Today it is fact that the bite is completely harmless. However, some tropic species (but not the large so-called "bird spiders") may introduce severe symptoms in humans when they get in non-avoidable contacts. The effects, which are due to neurotoxin within the saliva of the spiders, cover a broad range of symptoms: cramps, disturbances of the heart rhythm or even (in rare cases) paralysis of the breathing system and death. Antidotes are immune sera, muscle relaxants, calcium gluconate, cardiac supporters, etc.

   Important species are:
   - ***Cheiracanthium punctorium*** **(Europe)**: The bite occurs often during harvesting grass and other cereals and leads to a burning pain;
   - **Lycosidae (so-called wolf spiders)**: They introduce large tissue necrosis at the biting sites.
   - **"Bird spiders"**: The bite of so-called "bird spiders" is harmless, but their fine body hair (being scratched down by their hind legs) may harm eyes and skin of humans.

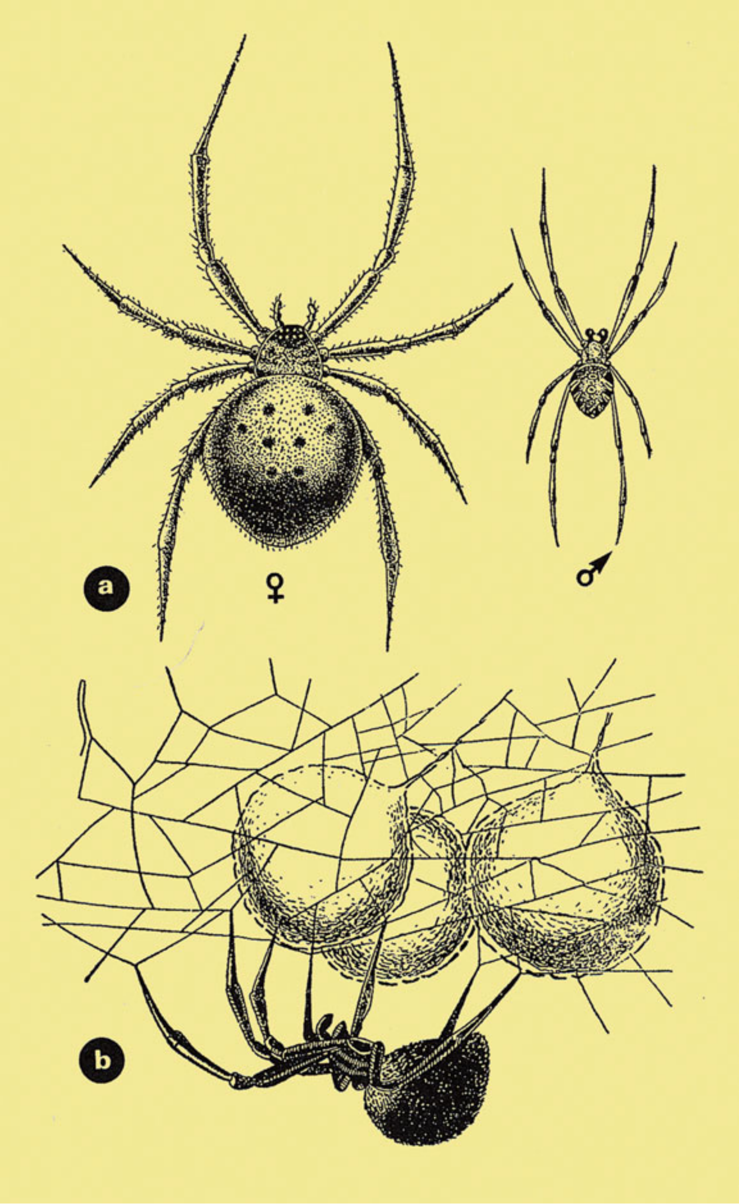

Fig. 5.2 European “black widow” spider (*Latrodectus tredecimguttatus*). Diagrammatic representation of the adults (**a**) and the female in the net with three cocoons

- **So-called comb spiders**: For example, members of the genus *Phoneutria* sp. in South America produce a poison with 13 components which have life-

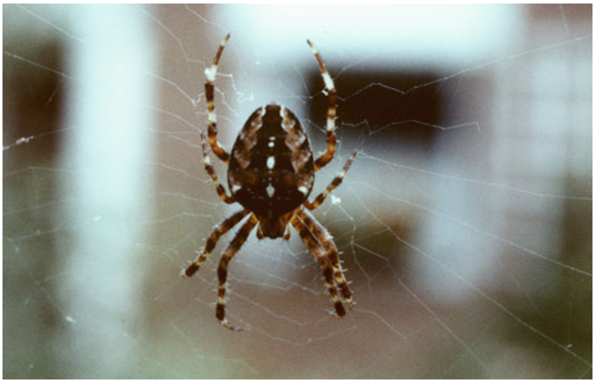

Fig. 5.3 Macrophoto of a garden spider (*Araneus diadema*) in its net (anterior and downwards)

threatening effects. They are occasionally imported to Europe within packages of bananas.
- ***Atrax*** species: In Australia, they enter human dwellings; especially the wandering males are much more dangerous than females, since they are very aggressive and their poison is six times more poisonous than that of the females.
- ***Loxosceles*** species: They are common and important in practically all countries of South and North America as well as are the species of the genus ***Harpactirella***.
- ***Latrodectes** species (**L. mactans, L. curacoviensis**)*: They are found in many warm countries around the globe and endanger humans and their pet animals. Their poison contains six toxic proteins that act neurotoxic. Death cases in Australia are rare (due to existence of an antivenom), but rather high in California and in several Southern states of the USA.

4. **Therapy**: The bites of spiders can be treated by intravenous application of calcium preparations, which decrease muscle cramps. Serum is effective even if it is injected only 60–80 h after the bite. Thus, it is always recommended to get information where sera against animal venoms are available in endemic regions or if having potential contact to venomous animals.

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5.3 Ticks

1. **Name**: The name is derived from the North German or Dutch word: *teken*, which means “to stick”, thus describing the way how ticks are attached to their hosts.
2. **Biology/morphology**: Ticks are as adults rather large arthropods reaching a size from 1 to 20 mm depending on the species. Their colour is species specific and ranges from yellow to dark brown, but they appear different when fully sucked reaching from olive-greenish to white and dark brown colour. Ticks are worldwide distributed and suck obligatorily blood at the skin surface of land animals and humans. As ectoparasites they are important vectors of agents of diseases. Very often they attack besides some main hosts a large spectrum of hosts (Table 5.1). For example, *Ixodes ricinus* was shown to attack more than 50 species of mammals, birds and lizards.

When starting blood sucking, the ticks show a dorsally-ventrally flattened, lens-like shaped and unsegmented body. Due to the uptake of large amounts of blood (up to 250 times of their original body weight in the case of females), their body is considerably enlarged. This is possible due to their extremely stretchable cuticle. At both of their lateral sides, there exists a so-called stigma plate, which is provided with numerous pores that are connected with the internal tracheal system, which allows transportation of oxygen throughout the whole body. The mouthparts are surrounded by a stick-like appearing apparatus including the cheliceres, which are able to cut hollows into the host’s skin, so that the whole anterior pole can be anchored in the skin. At each side of this anchoring and bloodsucking system, a so-called palpus is located, which consists of several segments, is covered by sensilla and is used by the tick as stabilization system while sucking blood.

Except for the larvae, which possess three pairs of legs, nymphs and adults have four pairs (see life cycles: Figs. 5.6 and 5.9). During walking, the first pair of the legs is stretched forward, since the so-called Haller’s organ (Fig. 5.11b) is located at the upper side containing a broad spectrum of sensitive nerve ends, which are used for orientation—especially in those species (like *Ixodes*), which do not possess eyes (Fig. 5.12). These sensilla are used to register body warmth of the hosts, CO_2 and various other specific odours excreted by potential hosts. The anus of the ticks is situated at the ventral side of the tick.

Female ticks lay large amounts (~ up to 18,000 depending on the species) of eggs onto hidden, semi-humid places on soil. The hatching larvae have six legs and start moult some weeks after a blood meal to become 8-legged nymphs, the number of which depends on the species. Furthermore, the number of nymph stages is different within the two groups of ticks:

– **Ixodidae** (hard ticks) develop only one generation of nymphs, while some species of the
– **Argasidae** develop up to eight stages by constantly repeated moults.

Table 5.1 Some common tick species (Argasidae; Ixodidae) and transmitted agents of diseases

Family/Species	Length (mm) of unfed adults	Hosts during development	Main hosts[a]	Disease (pathogen)[b]	Type of bite-transmitted pathogens
Ornithodoros moubata	m 8 f 10	Many	**Humans**	Relapsing fever (*Borrelia duttoni*)	S
Argas persicus	m 5.5–11 f 5.5–8	Many	Chickens	Fowl spirochaetosis	S
Argas reflexus	5–8	Many	Pigeons	(*Borrelia anserina*)	S
Otobius megnini	Fed nymphs 7–10	Many	Dogs, ruminants, horses, pigs, **humans**	Secondary bacterial infections	B
Ixodidae					
Ixodes ricinus	f 2.8–3.4 m 2.8–4	3	Dogs, cats, cattle, **humans**	Borreliosis Spring-summer encephalitis, Redwater (*Babesia divergens, B. microti*)	B V P
I. dammini[c] *I. pacificus* *I. scapularis*	As above	3 3 3	Deer, cattle, **humans**	Borreliosis Encephalitis, Babesiosis	B V P
Dermacentor marginatus	5	3	Many mammals	Tularemia (*Francisella tularensis*) Rocky Mountain spotted fever (*Rickettsia rickettsii*)	B R
D. reticulatus	5	3	Many mammals	Anaplasmosis Piroplasmosis (*Babesia canis, Theileria equi*)	A P
D. andersoni	5	3	Many mammals, **humans**	Anaplasmosis Piroplasmosis (*Babesia canis, Theileria equi*)	A P

(continued)

Table 5.1 (continued)

Family/Species	Length (mm) of unfed adults	Hosts during development	Main hosts[a]	Disease (pathogen)[b]	Type of bite-transmitted pathogens
Boophilus annulatus	f 2–2.5 m 2	1	Cattle	Texas fever (*Babesia bigemina*), Bovine piroplasmosis (*B. bovis*)	P
B. microplus	f 2–2.5 m 3	1	Cattle, equines	Q fever (=*Coxiella burnetii* = *R. burnetii*) Anaplasmosis (*A. marginale*)	R A
Amblyomma spp. *A. variegatum* *A. hebraeum*	f 6–7 m 5–6	3	Many mammals, **humans**	Tularemia (*Francisella tularensis*), Rocky Mountain spotted fever (*Rickettsia rickettsii*), Theileriosis	B R P
Hyalomma spp. *H. anatolicum* *H. marginatum*	4–6	2–3	Ruminants	Mediterranean Coast fever (*Theileria annulata*)	P
Rhipicephalus appendiculatus	f 2–4 m 4–5	3	Cattle, goats. Equines, dogs	East Coast fever (*Theileria parva*)	P
R. bursa	4	2	Cattle, goats, equines, dogs	Piroplasmosis (*Babesia ovis*, *B. canis*, *Theileria ovis*)	P
R. evertsi	4	2	Many mammals	East Coast fever (*Theileria parva*) Biliary fever (*Theileria equi*) Q fever (*R. conori*) Spirochaetosis (*Borrelia theileri*)	P P R S
R. sanguineus	f 2–3 m 2	3	Dogs, **humans**	Boutonneuse fever (*Rickettsia conori*) Piroplasmosis	P
Haemaphysalis punctata	f 2.8–3.5 M 2.5–3.1	3	Ruminants, **humans**	Meningoencephalitis, Piroplasmosis, Anaplasmosis	V P A

H. leachi leachi	f 2.8–3.5 m 2.5–3.1	3	Carnivores, small rodents	Canine piroplasmosis, Tick bite fever (*Rickettsia conori*), Q fever (*R. burnetii*)	P R R

m male; *f* female

A Anaplasma; *B* Bacteria; *P* Protozoa; *R Rickettsia*; *S* Spirochaetae; *V* Virus

[a] Hosts were selected according to important diseases; other hosts are possible

[b] These pathogens do not occur in all hosts and may also be transmitted by other tick species

[c] Some authors claim that *I. dammini* is *I. scapularis*

The single nymph stage of the Ixodidae and the last nymph stage of the Argasidae finally start the last moult to become the adult female and the adult male, respectively (Figs. 5.7, 5.8, 5.9 and 5.10). The time needed to become adult depends on several factors:

- The time to reach appropriate hosts to feed on as larva, nymph and/or adult
- Appropriate temperatures
- Appropriate humidity
- Appropriate quick finding of a sexual partner

For example, *Ixodes ricinus* ticks may develop within 178–2700 days. These data obtained in laboratory are surely somewhat different from those obtainable in nature, but show how resistant this species is in its struggle for survival being supported by their ability to starve for many months. In Europe, many *Ixodes* ticks run through their life cycle within 2–3 years due to large winter periods (Fig. 5.10).

The number of eggs that are produced by females depends on the species, temperature and the amount of ingested blood. *Ixodes ricinus* may depone 2000–5000 eggs, *Amblyomma hebraeum* (feeds on cattle) produces up to 18,500 eggs, *Argas reflexus* (the dove tick), however, produces only 20–100 eggs. Similar low numbers of eggs are produced by the tropical relatives of *Argas* belonging to the species *Ornithodoros moubata*.

Worldwide about 800 tick species exist, of which about 20 occur in Europe. The systematic position and their relationships are under controversial discussion since many years. Thus, there are several propositions to group the different tick species. Two of them are represented here in short versions:

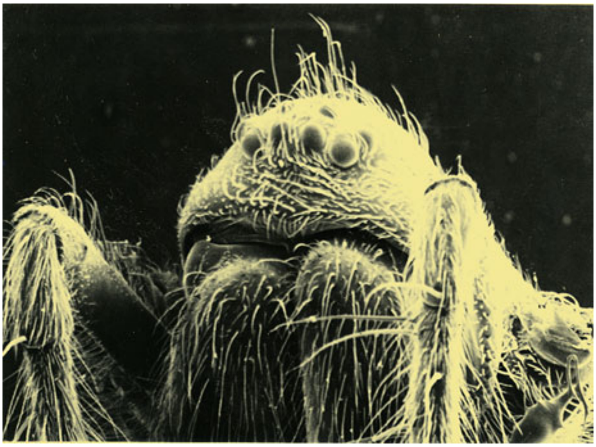


Fig. 5.4 Scanning electron micrograph of a spider showing its 8 eyes arranged in two rows

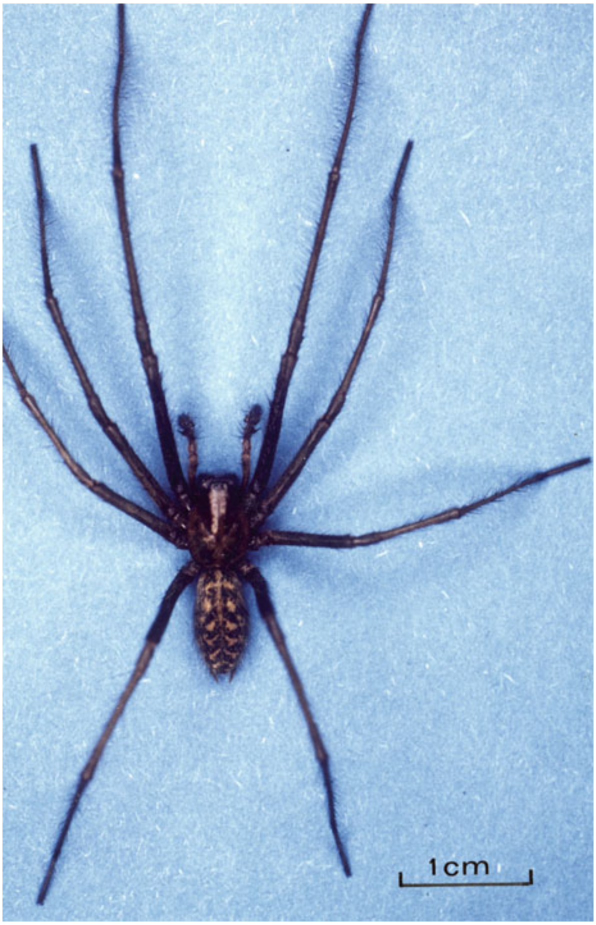


Fig. 5.5 Male of a hunting spider (*Tegenaria domestica*). Note the typical long palps

First Proposal

A. **Parasitiformes (ticks and mites).**
  1. **Order**: Ixodidae (ticks).
     Family: Ixodidae (ticks with a dorsal shield).
     Family: Argasidae (without a dorsal shield).

B. **Mesostigma (blood sucking mites).**
   Family: Dermanyssidae (bird mites).
   Family: Liponyssidae (rodent mites).

C. **Trombidiformes (gnawing mites).**
   Family: Demodicidae (mites inside the hair bulb).
   Family: Trombiculidae (harvest mites).

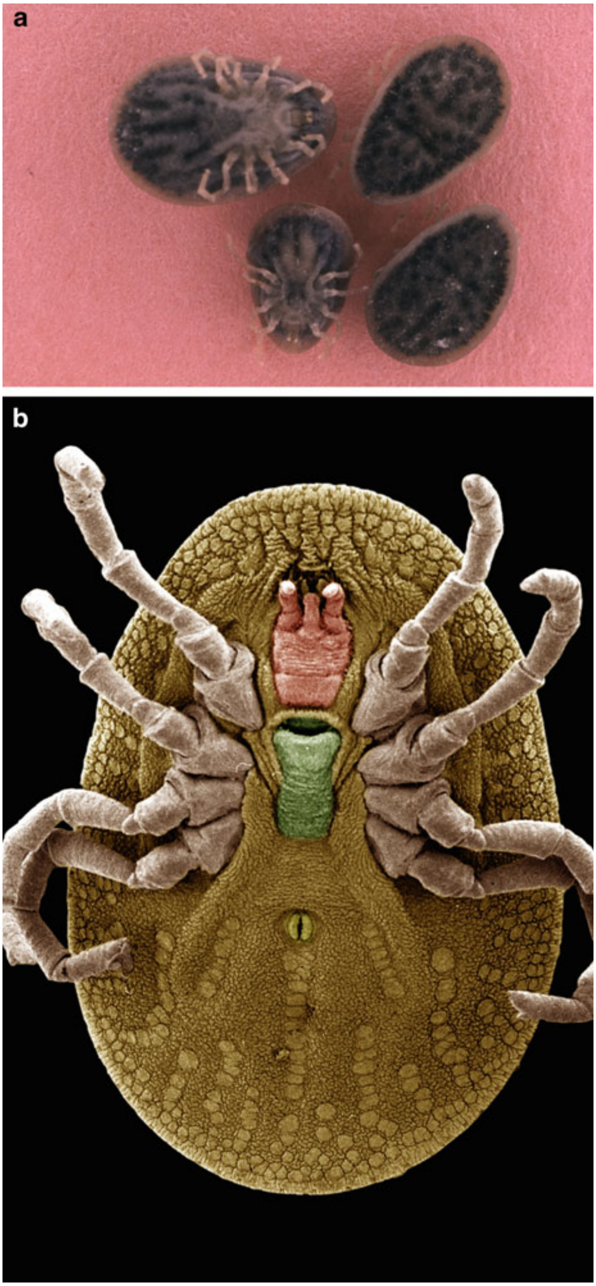


Fig. 5.6 Light (**a**) and scanning electron micrograph (**b**) of adult stages of *Argas reflexus*. (**c**) Diagrammatic representation of developmental stages of *A. reflexus*

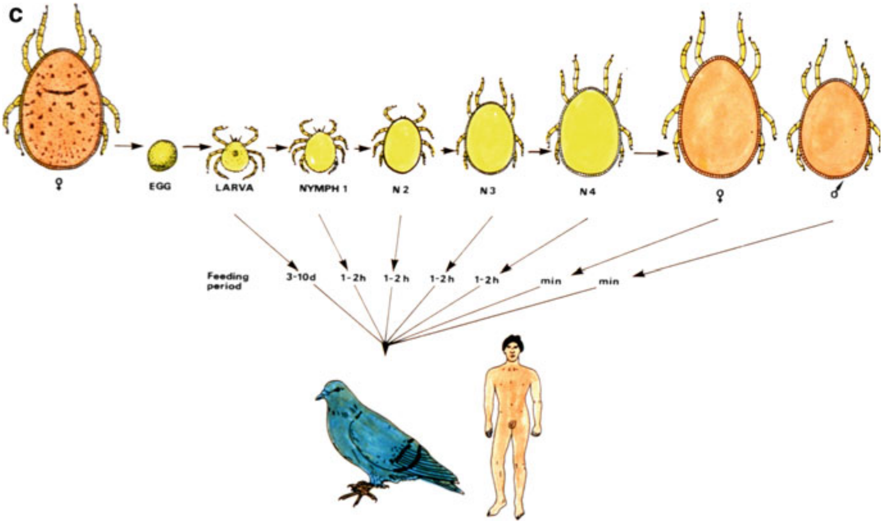

c
♀
EGG
LARVA
NYMPH 1
N 2
N 3
N 4
♀
♂
Feeding period
3-10d
1-2h
1-2 h
1-2h
1-2h
min
min

Fig. 5.6 (continued)

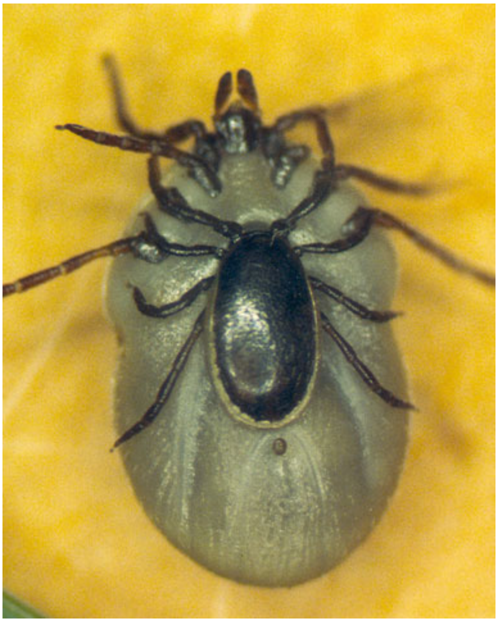


Fig. 5.7 Light micrograph of a fully engorged female of *Ixodes ricinus* in copula with a male

D. **Sarcoptiformes (scabies mites).**
   Family: Sarcoptidae (scabies mites).
   Family: Acaridae (stock mites).

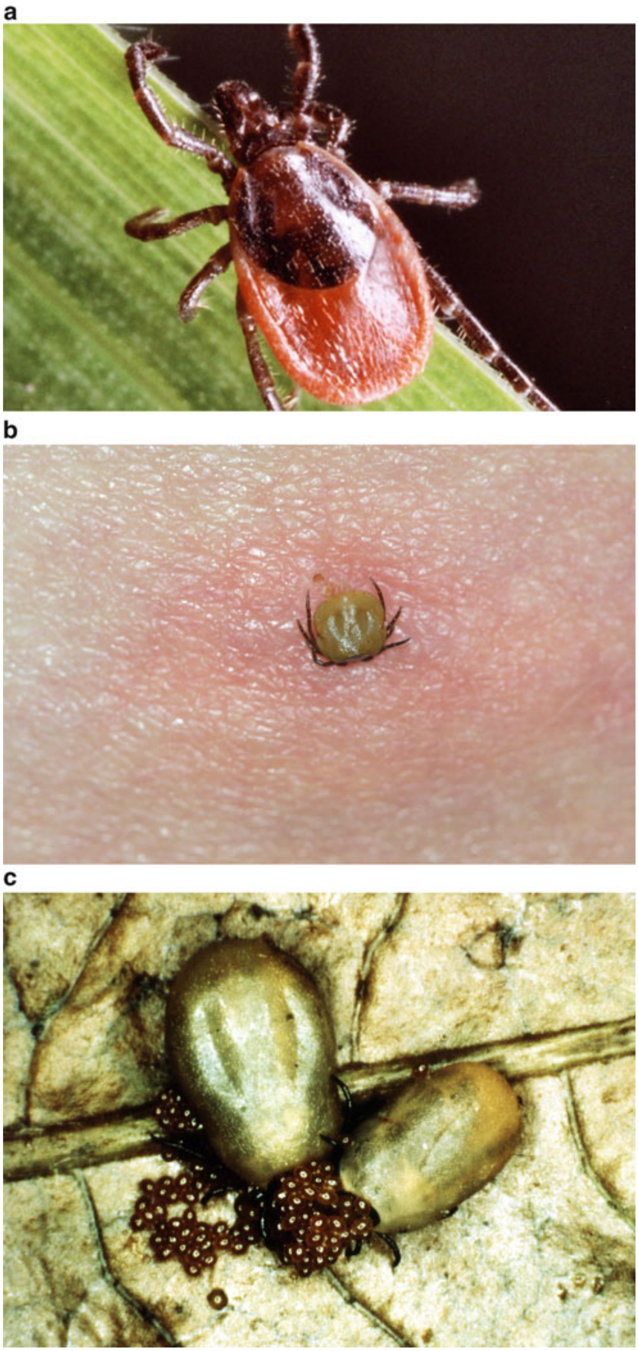


Fig. 5.8 Macrophotos of females of *Ixodes ricinus*: (**a**) unsucked stage lurking for a host. (**b**) Unsucked stage during sucking blood, nearly fully engorged. (**c**) Two females of *Ixodes ricinus* excreting large amounts of eggs

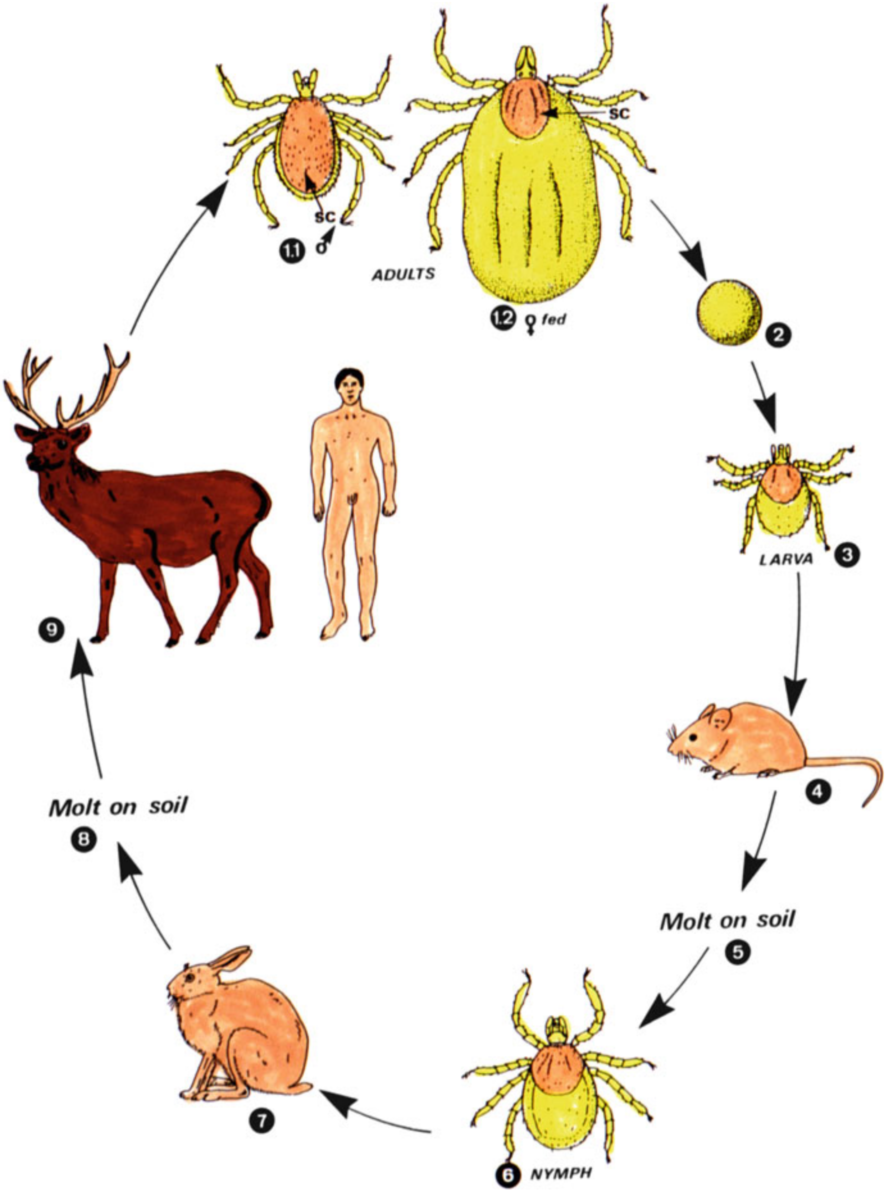

SC
SC
1.1 ♂
ADULTS
1.2 ♀ fed
2
LARVA
3
4
Molt on soil
5
6 NYMPH
7
Molt on soil
8
9

Fig. 5.9 Diagrammatic representation of the life cycle of *Ixodes ricinus* sucking blood at differently sized hosts during the life cycle. The different stages may suck besides at humans and mammals also at birds and reptiles if available in its biotope

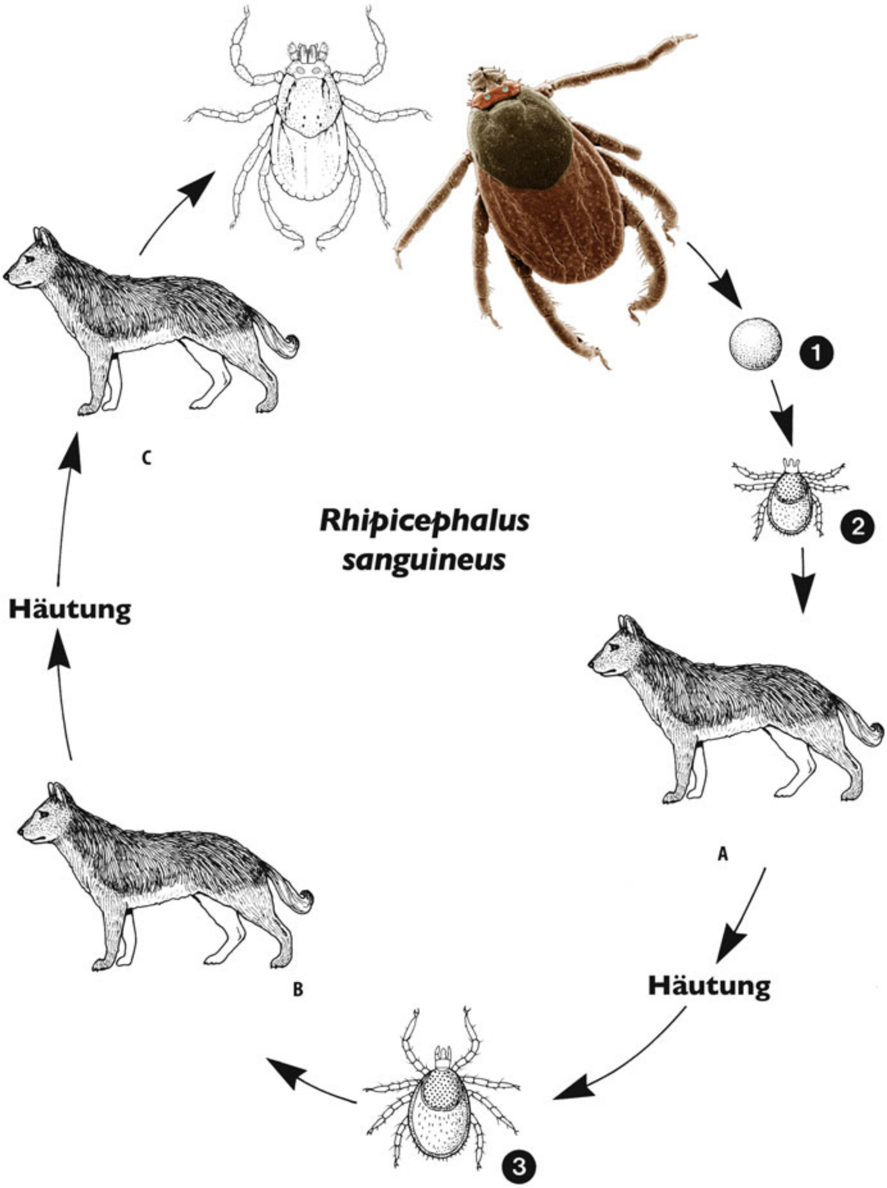

Rhipicephalus sanguineus
1
2
A
Häutung
3
B
Häutung
C

Fig. 5.10 Diagrammatic representation of the life cycle of the so-called brown dog tick *Rhipicephalus sanguineus*. This species has (like *Ixodes ricinus*) three hosts, since it leaves its host after each blood-sucking act. (**1**) Egg; (**2**) larva; (**3**) nymph; Häutung = molt

Other authors use the arrangement of the stigmata (=breathing openings) at the ventral side of the body as criteria for the classification:

Subclass: Acarina (Ticks and Mites)
Order: Metastigmata (ticks).
  Family: Argasidae (leather ticks).
  Family: Ixodidae (hard ticks, shield ticks).
Order: Mesostigmata (mites).
  Family: Dermanyssidae (bird mites).
  Family: Macronyssidae (rodent mites).
Order: Prostigmata (mites).
  Family: Demodicidae (hair bulb mites).
  Family: Trombiculidae (harvest mites).
Order: Astigmata (=Cryptostigmata).
  Family: Acaridae (stock mites).
  Family: Glycyphagidae (dust mites).
  Family: Sarcoptidae (scabies mites).

Due to these varying systematical considerations, this book only distinguishes roughly between **ticks** and **mites** in the following chapters.

The following key differentiates some common and important genera from each other.

Key for differentiation of some common and important genera

1a)	In the case of larvae, nymphs and females, the dorsal shield does not cover the whole back side but only anterior portions (Fig. 5.8a). In the case of males, the thick dorsal shield covers the whole backside (Fig. 5.7). The mouthparts are easily visible, when looking at the back side. The pair of stigmata are situated behind the coxae of the last pair of legs (Ixodidae, hard ticks)	**2**
1b)	The mouthparts of the adults are ventrally arranged and cannot be seen at the dorsal aspect, while they are visible at the six-legged larvae and 8-legged nymphs. In contrast to the Ixodidae, no back shield occurs. The larvae possess a tiny centrally located dorsal plate. The stigmata are situated between the coxae II and IV and are much smaller than those of the Ixodidae (Fig. 5.6a, b)	**5**
2a)	The anal furrow is situated before the anus	**Genus *Ixodes***
2b)	The anal furrow is situated behind the anus	**3**
3a)	Eyes are lacking; palps are shorter than the basis capituli; palp segment proceeds basis capituli	**Genus *Haemaphysalis***
3b)	Eyes are present; palps are as long as the basis capituli; second segment of the palps as long as broad	**4**
4a)	Small, mostly brown appearing ticks; their basis capituli appears with six corners	**Genus *Rhipicephalus***
4b)	Large, beautifully coloured ticks; the basis capituli looks rectangular	**Genus *Dermacentor***
5)	Dorso-ventrally flattened body with a sharp outer border	**Argasidae = leather ticks, genus *Argas***

Table 5.2 Differences between the two main families of ticks

Ixodidae	Argasidae
1. Cuticle is relatively hard	1. Cuticle is smooth and leathery
2. Scutum is present in all development stages covering the whole dorsal region of adult males, but only the small prodomosomal zone of larvae, nymphs, and adult females (*Ixodes*)	2. Scutum absent in all stages (*Argas*)
3. Capitulum anterior and always visible from dorsal view	3. Capitulum either subterminal or protruding from anterior margin of body larval stages
4. Spiracles of tracheal systems are located behind fourth coxae	4. Spiracles between third coxae
5. Mostly one pair of eyes, if present, situated dorsally on sides of scutum. The eyes consist of a single cuticular lens (no eyes in *Ixodes, Haemaphysalis*)	5. Eyes are usually absent (if present, on supracoxal folds)
6. Larvae, nymphs, and adult stages suck only once for several days	6. Nymphs and adults suck several times (in general for minutes), whereas larvae engorge for some days
7. Only one nymphal stage occurs in life cycle	7. Mostly 2 nymphal stages occur; in some species up to 8 are encountered
8. Males die after copulation which proceeds during the feeding act of females. Females die having laid the eggs on the soil (3000 eggs in *Ixodes*, 6000 in *Dermacentor*, 15,000 in *Amblyomma*)	8. Several copulation acts; several hundred eggs are laid on soil after each of the following feedings and copulation
9. Live mostly out of doors and only seldom in human dwellings; during life span species may attach consecutively to 1–3 hosts (species specific)	9. Live in farm houses, stables, nests of animals, etc., and attack their hosts during sleep

The characteristics of further worldwide or locally appearing ticks are listed in the two volumes published by Sonenshine and Roe (2014).

5.3.1 Hard Ticks (Ixodidae)

1. **Name**: Greek: *ixodes* = glueing.
2. **Examples of species** (see also Tables 5.1, 5.2):
   A. ***Ixodes ricinus***
      1. **Name**: Greek: *ixodes* = glueing; Latin: *ricinus* = like seed of this plant; English: wood tick, castor bean tick.

         Ixodes ricinus is the most common tick in Central Europe (Figs. 5.7, 5.8, 5.9 and 5.12). In eastern regions, it is replaced by *I. persulcatus*. *I. ricinus* is also found in North Africa and in the Middle East. In total, more than 50 mammal species in addition to humans are attacked by *I. ricinus*, which is also found on birds and reptiles. The 0.5 mm sized larvae hatch in spring time and parasitize mainly on small mammals, but also on birds and reptiles (especially often they are seen on blackbirds (*Turdus merula*) and garden lizards (*Lacerta agilis*). After moulting, the young now 1 mm sized nymphs attack many animals and humans. In contrast to larvae, the nymphs and adults possess four pairs of legs, which each have seven segments and terminal claws. The fully engorged nymphs proceed moult and become the 4 mm sized males of 5 mm sized females (Figs. 5.7 and 5.8). Copulation occurs mostly on the host, while the female is sucking blood. Afterwards the couple drops together onto the soil (Fig. 5.7) where the females start to lay eggs after 3–4 weeks (Fig. 5.9c). *Ixodes scapularis* in the USA has a similar life cycle, while *Ixodes canisuga* is found on dogs.

B. ***Rhipicephalus sanguineus* (Brown dog tick)**

1. **Name**: Greek: *rhipis* = fan; *cephale* = head; Latin: *sanguineus* = bloody.

   The adults measure as males 2 mm in length and as females 2.4–2.7 mm. However, engorged females reach a length of up to 12 mm. This species is worldwide distributed and it is suggested that it was spread all over Europe due to mass tourism and dog imports. In moderate temperatures, it develops mainly inside houses, while outside its propagation is restricted to the warm periods of the year. Inside houses they may become a real pest, since all stages also attack humans besides dogs and cats, where they are mainly found on the head, back, along the groins and between the toes (Figs. 5.10, 5.12 and 5.21).

C. ***Rhipicephalus bursa***

This species occurs on ruminants and uses only two hosts in its life cycle, i.e. larva and nymph stay on the same host.

D. ***Dermacentor reticulatus***

The specimens of this species, which recognize potential hosts by help of their eyes, have entered Germany coming from South European countries as a consequence of the increasing tourism. By the help of their eyes all stages (larvae, nymphs, adults) recognize their hosts quickly. Thus, hatched larvae are mostly able to reach the adult stage within 1 year, so that these populations increase considerably (Figs. 5.1, 5.12 and 5.22).

E. ***Dermacentor marginatus* (Sheep tick)**

This species enters recently Northern Europe coming from southern regions by the help of animal imports. It is most common on sheep, but also occasionally found on humans. Main activities occur in springtime (Fig. 5.22).

F. ***Haemaphysalis concinna* (Cattle tick)**

This species uses as larvae and nymphs small mammals, birds and reptiles as first host, but ruminants as final hosts (Fig. 5.22).

G. ***Haemaphysalis punctata*** has the same three-host life cycle and the same hosts lice *H. concinna*.

5.3.2 Argasidae (So-Called Soft or Leather Ticks)

A. ***Argas reflexus*** **(pigeon tick),** ***A. persicus*** **(chicken ticks)**

1. **Name**: Greek: *argas* = shiny.
2. **Life cycle**: These ticks are eyeless. Their females measure 6.5–11 mm, the males 5–7.5 mm, and the 4–7 nymph stages reach only 3.5–6.5 mm (Figs. 5.5 and 5.6). The copulation takes place on the floor and the females lay 4–6 times about 80–100 eggs. The bloodsucking process is short (mostly 15–20 min; however, larvae suck for up to 1 week), but is repeatable several times. They stay hidden in bird's nests and chicken stables, but also in human dwellings, where they feed on humans. These so-called leather ticks may starve for years and thus may reach a lifespan of more than 10 years. *Argas* (*Persicargas*) *persicus* attacks in Russia, Africa, Eurasia birds and humans, is able to transmit *Anaplasma* and *Borrelia* species and may induce paralysis.
3. **Symptoms of bites**: The biting sites at human skin appear as bluish and develop itching papulae (erythemas), which may be followed by skin swellings, fever and eventually by severe urticarial, bronchial damages and eventually sudden unconsciousness.

B. ***Ornithodoros*** **species**

1. **Name**: Greek: *ornithes* = birds; *doros* = leathern sack.
2. **Life cycle**: The life cycle of the species of this genus (Table 5.1) is similar to that of *Argas* species having mostly five nymphal stages. However, larvae do not feed, but moult still inside the egg to become nymph 1. The nymph stage 5 develops into the ♀ or ♂ adult.

   Important species are:

   - *Ornithodoros moubata* (eyeless tampan) lives (also in houses) in dry regions of Southern Africa and attacks many animals besides humans (Table 5.1).
   - *Ornithodoros savignyi* (eyed tampan, sand tampan) has two pairs of eyes and is found in arid regions of Africa, Arabia and India. It attacks humans besides horses, camels and cattle. However, it is not an important vector of agents of disease.
   - *Ornithodoros erraticus* (North African tampan). This species (vector of the African pig pest fever) occurs in North Africa and also in Portugal and Spain.

3. **Symptoms of bites**: Besides severe losses of blood due to the large size of these ticks, they may transmit agents of severe diseases (see Table 5.1). The species of the *O. moubata* complex are vectors of the agents of the so-called **endemic relapsing fever** due to *Borrelia duttoni*. Only the nymphs transmit these stages within the saliva; the adults excrete them within coxal excretions.

C. ***Otobius megnini***

Name: Greek: *otos* = ear. This species occurs in North America, Africa and India and reaches as adult a length of up to 12 mm. However, adults do not feed at all, while the larvae and nymphs suck blood at vessels mainly in the ears of horses, cattle and occasionally at the body of humans. Transmission of agents of disease may occur, but only mechanically, since no peculiar cycles are known (Fig. 5.22).

5.3.3 Skin Reactions After Tick Bites

Ticks find their hosts by the help of their eyes and/or by activity of the so-called **Haller's organ** smelling the host's body odours (Figs. 5.11b, 5.12). Then they attach themselves to the body of their hosts by entering their tube-like hypostome, which consists of an outer sheath and two inner cheliceres, provided to cut hollows into the epidermis and dermis (Figs. 5.13 and 5.14). Then the saliva is injected into this hollow lacuna (pool), which becomes filled by blood. The saliva–blood mixture remains fluid, since the saliva contains lytic substances, peculiar enzymes and anticoagulants. Especially the injected prostaglandins help to keep the blood fluid for the blood meal that goes on permanently for up to 10 days. The species of the Ixodidae possess longer mouthparts than the Argasidae, which suck blood only for a short time (~20 min) (Figs. 5.6a, 5.13 and 5.14). The ixodid ticks excrete during the early phase of attachment substances, which harden and thus fix the tick at the skin of its host. The active substances needed for this fixation are produced by two types of glandular cells. This procedure is best documented in the case of *Boophilus microplus* ticks. Lipoproteins are first excreted, which harden and form ring-like stabilization systems. Starting after 5 min and finishing after 24 h a solid tube (**internum**) is formed. Then the salivary glands of the ticks excrete proteins and carbohydrates, which together produce another layer called **cortex**. Both structures fix the ticks at the host's body, so that blood sucking is undisturbed.

Blood sucking is species and genus specific with respect to timing and duration. While females of *Argas reflexus* suck once per month for 15–30 min, their larvae need 5–10 days, but their nymphs take blood only for 1–2 h. The larvae of *Ixodes ricinus* suck for 3–5 days, the nymphs for 3–7 days and the females for 7–14 days, whereby they ingest up to 200–250-fold their own body weight, which increases from 1.5–2.5 mg up to 250–400 mg (Figs. 5.8, 5.15). The bites of ticks are painless and are mainly only noted by the occurrence of a feeling of itching—if at all. The biting site appears mostly slightly red (Fig. 5.8), but occasionally symptoms of necrosis occur. In the case of *Argas reflexus* and other related species haemorrhagies measuring some centimetres in diameter may occur.

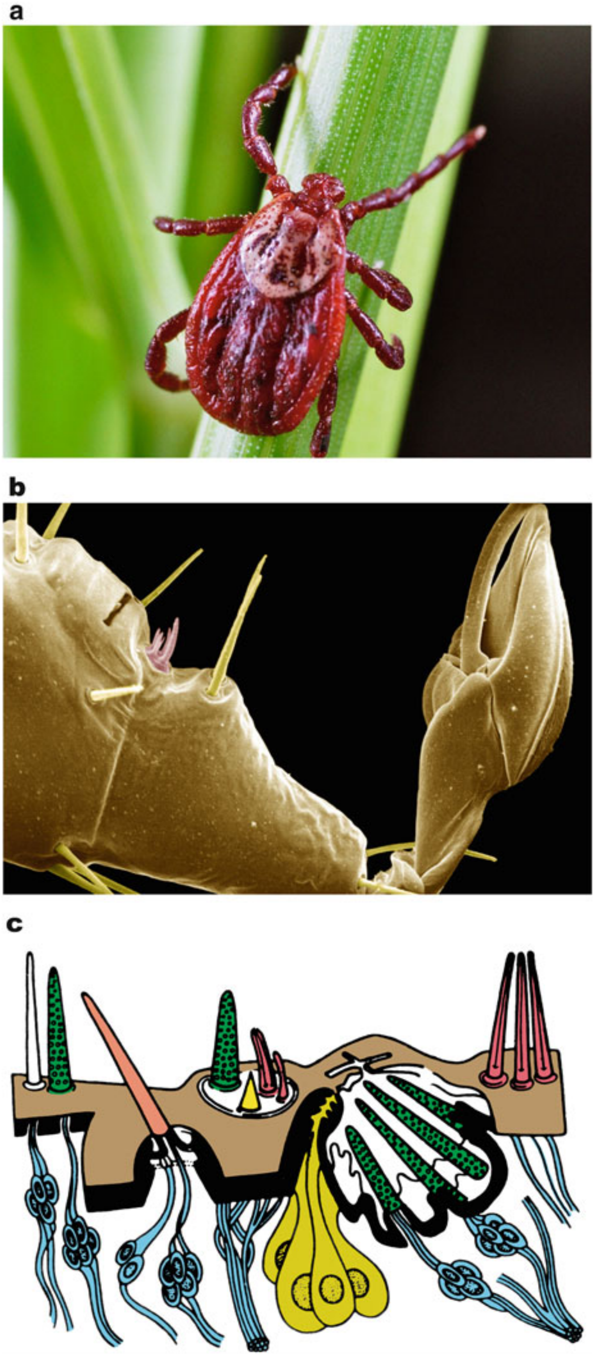


Fig. 5.11 (**a**) Macrophoto of a female of *Dermacentor reticulatus* lurking for hosts. (**b**) Scanning electron micrograph and (**c**) diagrammatic representations of the so-called Haller's organ, which is composed of several types of receptor cells being connected to the nerve system

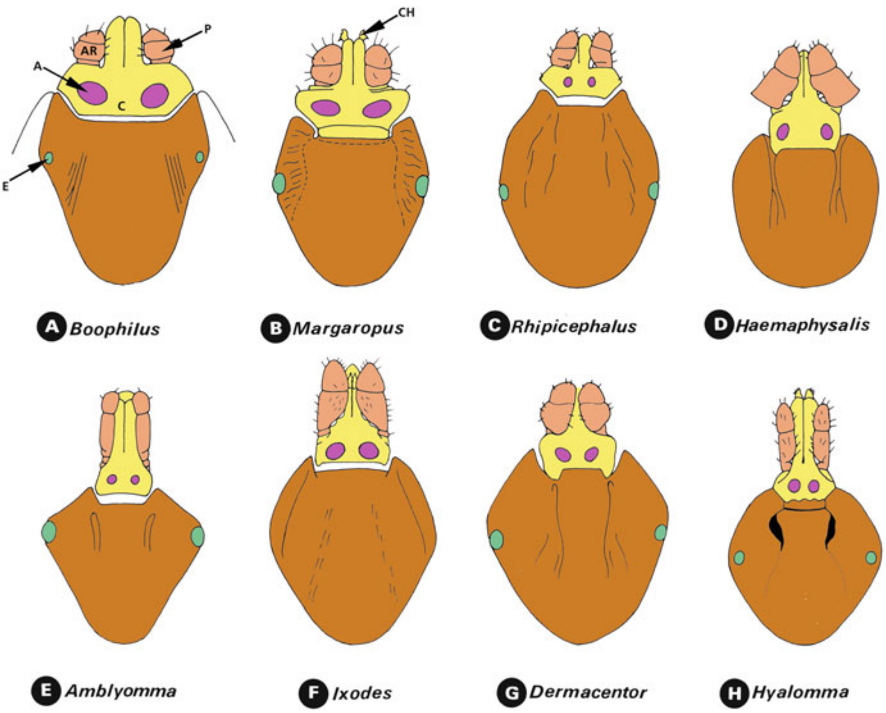


Fig. 5.12 Diagrammatic representation of the anterior ends of specimens of different hard tick genera. These species which possess eyes are able to approach their hosts by walking, while eyeless species have to wait until potential hosts get in contact with plants onto which they are lurking. *A* area porosae = plate with pores; *AR* basic segment of the pedipalpus; *CH* chelicere; *E* eye; *P* pedipalpus

5.3.4 Tick Paralysis

Paralysis may occur when the specimens of some tick species start their blood meal and inject their saliva in order to keep the host's blood fluid. The grade of paralysis depends on

- the amount of the saliva injected,
- the tick species,
- the site of the body, where the "poisonous" saliva is injected.

Peculiar severe cases (including death) have been reported in the case of bites of *Ixodes holocyclus*, which is found, e.g., in Australia and South Africa. However, cases of human tick paralysis due to several ticks have been reported worldwide (rarely also in Central Europe). The symptoms start by paralysis of the legs and wander up to the arms. If heart, neck, lung and breast muscles are involved, death

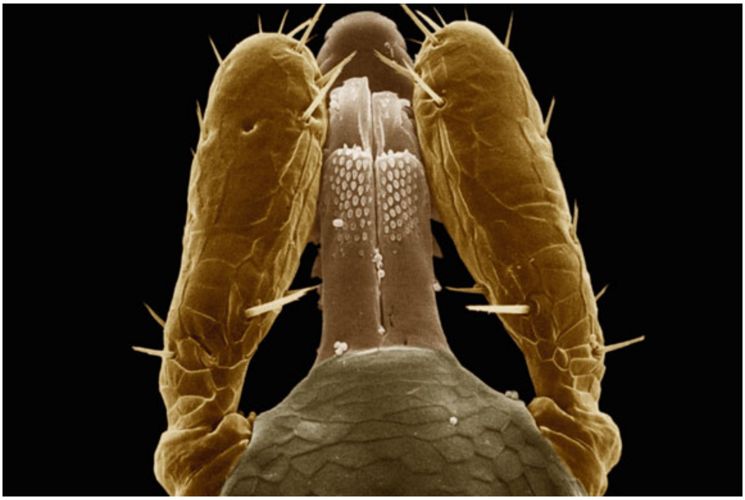


Fig. 5.13 Scanning electron micrograph of the anterior end of the tick *Ixodes ricinus* showing the hypostome (with many teeth) and the two pedipalps. The cheliceres are somewhat protruding from the hypostome. The hypostome is entered into the skin and the two pedipalps fortify the body at the host's surface thus fixing the tick there for several days

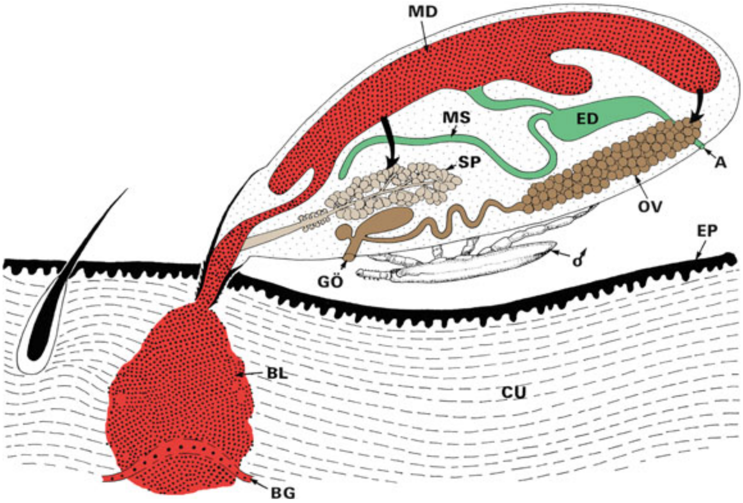


Fig. 5.14 Diagrammatic representation of a feeding female ixodid tick. The *arrows* indicate transportation pathways of agents of diseases. Note that the tick engorges blood cells and lymph present within spaces of the tissues. *A* anus; *BL* interstitial blood cells; *BG* blood vessels; *CU* cutis; *ED* hind gut; *EP* epidermis; *GÖ* genital opening; *MD* midgut filled with blood cells; *MS* Malpighian tubules, excretory system; *OV* ovary; *SP* salivary glands

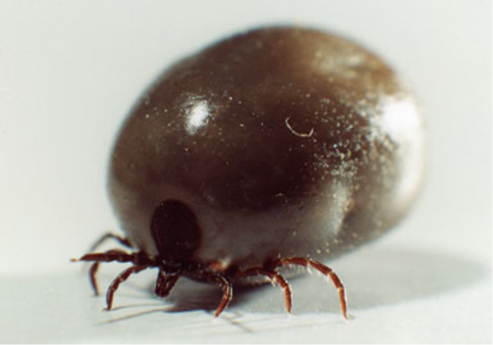


Fig. 5.15 Macrophoto of a fully engorged female tick of the species *Ixodes ricinus*

may occur. The efficacy of the toxin is not yet completely understood. If the sucking tick is removed, the endangering symptoms are reduced and disappear within a few hours.

5.3.5 Treatment of Tick Bites

The strong hooks of the hypostome (Figs. 5.13, 5.15) anchor the sucking tick firmly at the skin of their hosts. Rough attempts to remove the thus anchored tick from its host would disrupt the tick and potentially introduce the agents of disease that are inside the tick. The best way to remove an attached tick is to use very pointed tweezers that allow to grasp the hypostome of the tick and thus to remove it without pressure on its body, so that potentially included agents of disease are not pressed into the bite channel. The formerly recommended advice to cover attached ticks with oil or alcohol should no longer be carried out, since it has been shown that these procedures increase the release of potentially infectious saliva. Once ticks are removed without disruptions, the bite site can be treated with cooling products and antihistamine ointments.

5.3.6 Transmission of Agents of Disease

Tick attacks are not dangerous due to the loss of blood, but due to the potential transmission of agents of diseases such as viruses, bacteria, rickettsiales and/or parasites (see Table 5.1). Before agents of disease are transmitted to humans or animals, such stages can be transmitted to the tick eggs and thus become enriched in the tick population. Principally must be differentiated between **transstadial transmission** (i.e. transmission from larvae to nymphs and finally to adults) and **transovarian transmission** (i.e. from the female tick to its progeny via eggs). Both pathways are especially important in the case of viruses, since both pathways lead to a constantly increasing infection of the ticks in a given biotope. Until today more than 20 species of so-called arboviruses (=*arthropod-borne viruses*) are known (Table 5.2).

5.3.6.1 Spring–Summer Meningoencephalitis

In the year 1948, the first infected ticks bearing this tick encephalitis virus were described. It occurs in mice and other non-diseased animals in northern countries of the Balkans, Austria, Switzerland and Southern to Central Germany reaching infection rates of up to 5 % among *Ixodes ricinus* ticks. Recently, the Russian version of this virus—transmitted by *Ixodes persulcatus*—is on its “march” to the West and has already reached East Germany.

(a) **Symptoms of disease**:

After a symptomless incubation period of 2–28 days follows the **first phase** of the disease (for 1–8 days) being characterized by fever (often more than 39 °C) and several very unspecific symptoms such as fatigue, headache and body pain which erroneously were kept for symptoms of a so-called “summer flu”. After this phase, a fever-free period follows for 1–20 days, before the **second phase** of the disease starts, which is based on the invasion of the viruses into the brain. The following symptoms may occur (simply or in combination): vomiting, fever higher than 40 °C, light sensitivity, sight defects, paresis and heart rhythm disorders. All these clinical symptoms may lead to a lethal phase of meningoencephalitis, meningitis or meningocephalomyelitis. Especially young children and old persons are endangered by death. Fortunately only 10 % of the infected persons enter the second phase. About 23–50 % of the infected persons do not show the symptoms of the first phase and thus are surprised by the initiation of the severe symptoms of the second phase. The **second phase** of the disease may comprise three different groups of symptoms:

1. 50 % of the infected persons show the signs of a meningitis (=inflammation of the meningeal covers).
2. 40 % suffer from a meningoencephalitis: a combined inflammation of the brain and of the meningeal covers.
3. 10 % show the symptoms of a myelitis (nerve inflammation).

Several persons of any of the above-listed three groups suffer additionally from a painful inflammation of nerve endings (**radiculitis**). Depending on the intensity of the infection, the spring-summer meningoencephalitis may have severe consequences for infected persons:

- 30 % of the patients may be severely struck by paresis and by a total or partial loss of hearing.
- 3 % remain unable to move and need a wheelchair for the rest of their life.
- 12 % of the patients die after a short or long phase of severe disease.

Even persons, who finally do not belong to one of the three above described groups, may need a long recovery period in hospital, where they may be attacked by other infectious diseases. In the case of the **Russian meningoencephalitis**, lethality may even reach levels of up to 25 %.

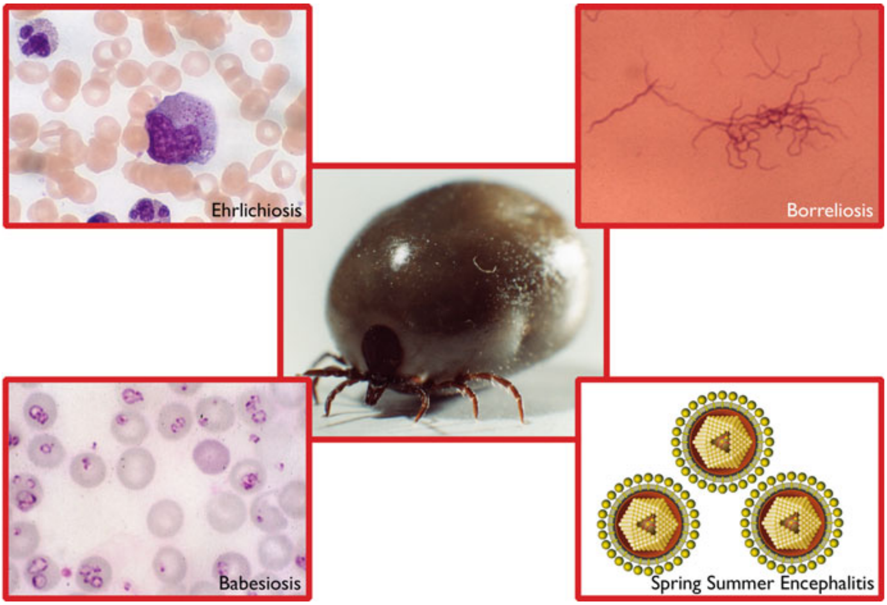


Fig. 5.16 Representation of important agents of diseases transmitted by *Ixodes ricinus*

(b) **Prevention**

Since curing therapy measurements are practically not possible after an outbreak of a meningoencephalitis, protective vaccination is strongly recommended for people living in endemic regions. In Germany and Austria two vaccines (to be used in three steps) are available (FSME-Immun® and Encepur®), which also protect from the Russian strain of the virus. Furthermore, it is highly recommended to use tick repellents (e.g. Viticks®).

5.3.6.2 Lyme Borreliosis

Spirochaetes of the genus *Borrelia* (Fig. 5.16) are important agents of diseases of humans. These bacteria reach a size of 10–30 × 0.3–0.6 μm, are characterized by 4–10 contorted windings, show 7–10 peripheral fibrils and are covered by a mucous layer. During an epidemic among people in a small village named Lyme in Connecticut the Swiss scientist Burgdorfer detected in 1982 this bacterium as the agent of a widespread disease which at first was called **Lyme disease** (now **Lyme borreliosis**). These bacteria are transmitted worldwide by various tick species of the genus *Ixodes* (e.g. *I. dammini* = *I. scapularis; I. ricinus, I. persulcatus,* etc.). During the years until 2000, it was shown that this disease occurs worldwide. Since the symptoms are highly variable (especially in later phases of the disease), different names had been previously introduced: 1909: **erythema chronicum migrans**; 1883/1902: **acrodermatitis chronica atrophicans**; 1922: **meningopolyneuritis** or 1943: **lymphadenosis cutis benigna**.

All these features of disease are now proven to have their origin in infections with strains of *Borrelia burgdorferi sensu strictu* and various other related species (e.g. *B. garinii, B. afzelii, B. spielmani*). The infection rates of *Ixodes* species with *Borrelia* species are high and reach 20–30 % in many regions. However, it was shown that severe symptoms of disease occur much less often in animals than in humans, since more than 90 % of animal infections are mostly not noted (but are detectable by the presence of antibodies). Infected ticks may be transported by animals (mice, rats, roe deer, birds, etc.) into new biotopes, which all are characterized by the presence of humidity, shadow, grass, ferns, low bushes, foliage, etc., so that important tick hosts such as mice can live and survive there.

Transovarian transmission is common in ticks, so that their next generation is often already infected. Bloodsucking insects have apparently only a low importance as vectors, although it cannot be excluded that the rough mouthparts of, e.g., tabanids might be contaminated with such bacteria. **Animal reserve hosts** such as "mice" (*Apodemus, agrarius, A. flavicollis, Clethrionomys glareolus, Peromyscus leucopus*), but also chipmunks and meadow voles, etc., are important to keep up high infection pressure in many regions, while cattle suppress infections and thus eliminate bacteria from their biotope. Humans become infected during working or wandering in tick-infested biotopes or even in their own garden if infected mice have imported ticks. The infection with *Borrelia* stages occurs by injection of the saliva of the tick. The bacteria live and reproduce themselves in the tick's intestine (Fig. 5.16). As soon as a tick ingests blood, the bacteria start divisions inside the intestine. After about 16–48 h, they enter into the haemolymph of the body cavity and penetrate finally into the salivary glands. If attached ticks are removed within 12–16 h after attachment (without squeezing them) an infection with *Borrelia* stages is prohibited. This is different from infections with spring-summer viruses, which are transmitted immediately after the beginning of the bloodsucking act. *Ixodes* nymphs suck permanently for about 3–7 days, females for 7–14 days, and males suck only for very short periods. The bacteria are distributed with the bloodstream into all organs, but stay in considerable high numbers close to the bite site, where an intense reddening may occur (Fig. 5.9).

The symptoms of borreliosis vary considerably. Therefore serological tests are essential. However, they are only positive starting about 4–5 weeks after an infection. The first significant and often occurring symptom of a tick-borne *Borrelia* infection is a wandering **erythema chronicum migrans** (**ECM**), which starts at the biting site about 1–3 weeks after the tick has been attached there. This red (often large) spot (Fig. 5.17) may wander along the skin surface of humans, decreases in intensity and disappears finally within 3 weeks up to 3 months. During this phase of the "red rush", fever occurs as well as headache and weakness. Unfortunately serological investigations remain negative for weeks, if not an older infection had produced antibodies which are still present in low numbers. Most cases of ECM are diagnosed in late summer and autumn. Children very often show the symptoms of **lymphadenosis cutis benigna (LCB)** (Fig. 5.17) in addition or after the symptoms of **ECM**. Enlargement of the lymphatic system occurs often along the ears (Fig. 5.17c). The symptoms of the above-described **phase 1** of the borreliosis

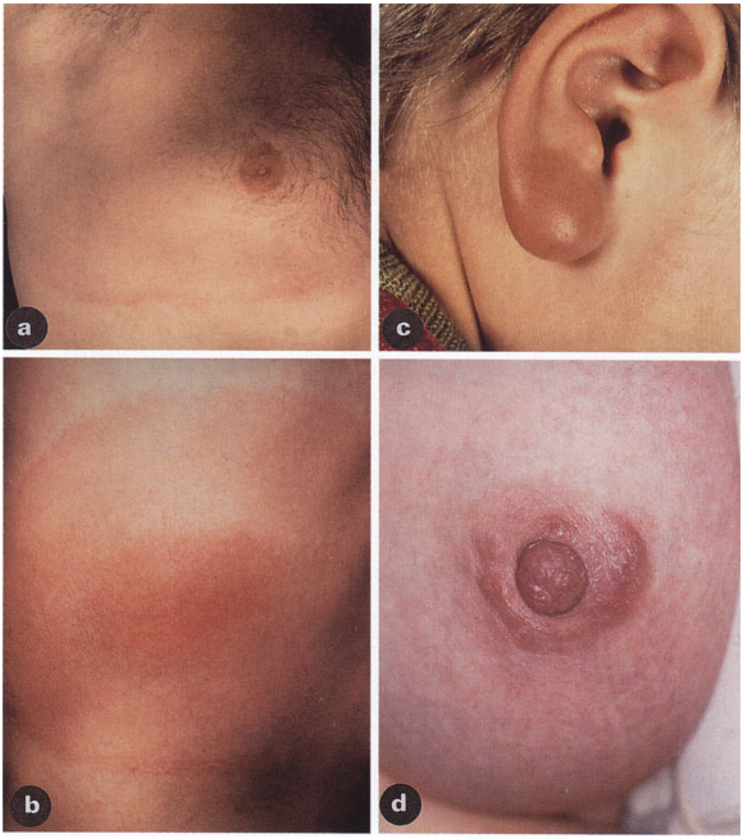


Fig. 5.17 Photos of skin reactions of persons infected with bacteria (*Borrelia burgdorferi*). The so-called **Lyme borreliosis** has a broad spectrum of symptoms. (**a**, **b**) The incubation period of the **erythema chronicum migrans** is about 2–3 weeks; it may, however, vary between 2 days and 3 months. It starts by the appearance of a red spot at the biting site and becomes later concentrally enlarged. (**c**, **d**) In the case of **lymphadenosis cutinea benigna (LCB)** reversible benign swellings of the lymph system are leading symptoms, e.g. at the ear (**c**) and/or at the breast (**d**)

may disappear spontaneously or proceed after weeks into the **second phase** of the disease. Sometimes the second phase may start 1–7 months after the infection without a previous first phase. The second phase is characterized by neurological symptoms, e.g. by meningopolyneuritis (MPGBB), which is accompanied by a paresis of the facial nerve or by inflammations around eye nerves in addition to muscle pain. Inflammations of the heart muscles are also common. The **third phase** of the disease, which may start about 6 months or even years after the initiating tick bite, is characterized by the occurrence of an **acrodermatitis chronica atrophans (ACA)**, which is characterized by a painful, chronic dermatosis along arms and legs and by myelitis and different versions of arthritis. Furthermore, the brain may suffer from several intense damages. During the different phases, serological diagnosis may show infections by *Borrelia* stages. However, after years the infections of the spinal cord show only very low antibody titres.

The **therapy** of **human borreliosis** is based on high dosages of antibiotics:

- **Penicillin**: 4.5 million units orally for 14–21 days in the case of adults;
- **Doxycycline**: 2 × 100 mg per day for 14–21 days (children below an age of 12 years: **amoxicillin**);
- **Macrolids**: in the case of allergic persons.

Drug therapies in late phases of the disease are rather useless, since then the bacteria have disappeared and only the organ damages have remained.

5.3.6.3 Further Tick-Transmitted Agents of Disease

1. ***Borrelia duttoni*** is the agent of the so-called **endemic relapsing fever** or **tick-borne relapsing fever**, which is found in Africa, India, regions of Asia and in Central America. In Central Europe, it is practically absent. These *Borrelia* stages are transported during sucking acts of specimens of ticks of the genus *Ornithodoros*. The bacteria are transmitted by blood or lymph fluid to the different organs of humans, where they start reproduction processes and thus induce fever. After an incubation period of about 1 week, fever occurs for 3–7 days, followed by 1 week of normal body temperatures. The initially rather high fevers decrease during the next 5–10 fever phases due to the increasing activity of the immune system. If no complications occur, the disease stops without treatment. The **diagnosis** can be done by serology, by the help of blood smear preparations or by thick-droplet probes during the fever phase. For **therapy**, penicillin, tetracyclines or chloramphenicol can be used. Since the availability of these compounds, the lethal cases have been reduced considerably.
2. **Viruses** transmitted by *Ixodes ricinus* may induce a disease in sheep and humans, which is called **louping ill** (turning disease).
3. ***Rickettsia rickettsii*** is the agent of the so-called **Rocky Mountain spotted fever** which is transmitted by *Dermacentor andersoni* ticks, which ingest these agents of disease while sucking at reservoir hosts such as rodents or wild goats (Fig. 5.19). The stages of this *Rickettsia* species also infect the eggs of the tick so that the next generations become infected. The disease occurs besides in North America also in regions of South America, but the symptoms are highly variable. After a tick bite, the incubation period may take 6–7 days. Then follow persistent high fevers for 2–3 weeks and the typical further symptoms of the typical **spotted fever** except for the skin reactions, which in this case are much more severe due to a necrotic vasculitis. This vasculitis occurs also in inner organs such as heart and brain and thus induces a high lethality. **Therapy** can be done by application of chloramphenicol or tetracycline, which reduce the originally high rates (up to 20 %) of lethality.

4. ***Coxiella (Rickettsia) burnetii*** occurs worldwide in sheep. Humans are occasionally infected by *Dermacentor marginatus* ticks or by inhaling *Rickettsia* stages within excretions of sheep (Fig. 5.20).
5. ***Rickettsia conori*** is the agent of the so-called African tick bite fever and **Boutonneuse** or **Marseille** fever, which occurs in the coastal regions of the Mediterranean Sea and is transmitted by the dog tick *Rhipicephalus sanguineus* (Fig. 5.10). The biting site forms a primary lesion, which appears as a blue or blackish dot (Figs. 5.18, 5.19 and 5.20). After an incubation period of about 7–9 days high-grade fever occurs for 8–14 days, which is accompanied by headache and pain at the back and along the joints. **Treatment** can be done by the use of tetracyclines.
6. ***Pasteurella* (*Francisella*) *tularensis*** is a bacterium, which is endemic in Russia, Japan and regions of North America. Reservoir hosts are hares and rabbits. Besides ticks also fleas and tabanids may transmit these bacteria. Especially endangered are those persons, who get in contact with hares and rabbits (e.g. hunters). This agent of disease is highly contagious, so that the uptake of only a few bacteria is sufficient to induce a strong pulmoniasis. Besides the bites of bloodsucking ticks or insects, the agents of disease may also be transmitted by inhalation, perioral or via skin lesions. At the bite site, a papula becomes prominent and may develop an ulcer. The **diagnosis** can be done by the help of serologic methods or by the use of cultural methods. **Therapy** is best done using streptomycin.
7. **Babesiosis** can be found in dogs and humans. These protozoan stages are transmitted by ticks. *Ixodes ricinus* transfers *Babesia microti* from rodents to humans, while *Babesia canis* can be transmitted even by two tick species (in Germany: *Dermacentor reticulatus*, in South Europe: *Rhipicephalus sanguineus*). The disease may be lethal due to the ongoing destruction of the invaded red blood cells.

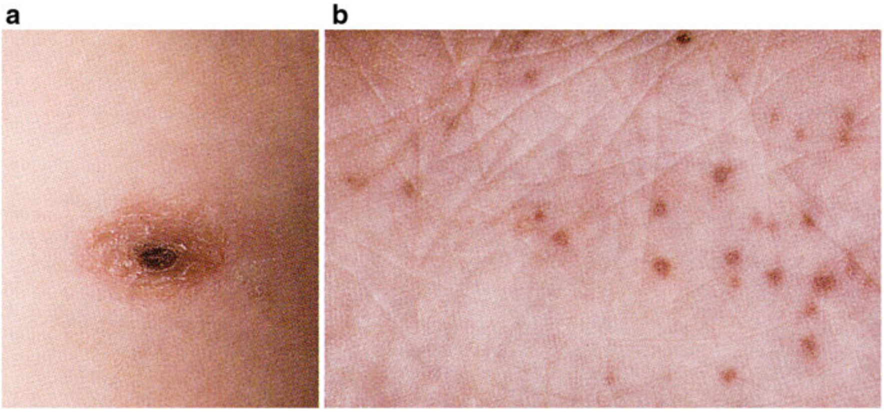
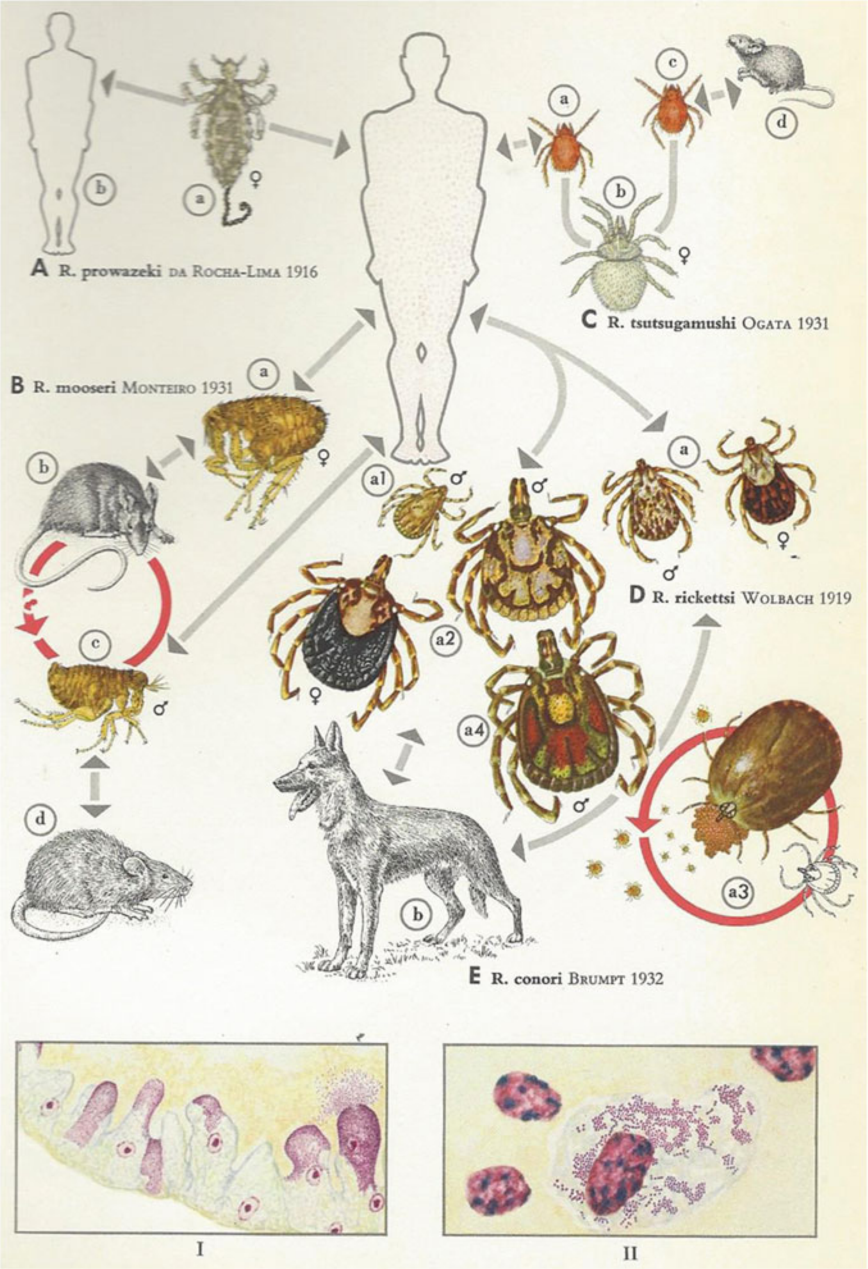


Fig. 5.18 Symptoms after transmission of rickettsiae. (**a**) *Tache noire* respectively *T. bleue* after infection with *Rickettsia conori*. (**b**) Generalized exanthema after a rickettsiosis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C R. tsutsugamushi OGATA 1931
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Fig. 5.19 Diagrammatic representation of the transmission activity of ixodid ticks, mites and lice. (**A**) ***Rickettsia prowazeki*** **Da Rocha-Lima 1916**. The cause of petechial typhus. (**a**) Vector: the louse *Pediculus humanus* (via faeces). (**b**) Man—as the reservoir host. **Infection series**: man–louse–man. (**B**) ***Rickettsia mooseri*** **Monteiro 1931**. The cause of murine typhus fever. (**a**) Vector: the flea *Xenopsylla cheopis* (faeces). (**b**) The house rat as the reservoir host. (**c**) The rat flea *Xenopsylla cheopis* as the vector. (**d**) Migratory rats as reservoir hosts. **Infection series**: migratory rats–fleas–house rat–flea–man. (**C**) ***Rickettsia tsutsugamushi*** **Ogata 1931**. The cause of

5.3.7 Protection from Tick Bites

Infestation with ticks occurs mainly outside of human dwellings (except for *Rhipicephalus sanguineus* stages). Protection from bites can be achieved by the use of tick repellents such as Viticks® or Autan®. For dog protection several products are available that are dropped along its backline and stay there for up to 6 weeks. (e.g. Advantix®, Exspot®).

5.3.8 Further Reading (Tick)

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Fig. 5.19 (continued) Tsutsugamushi fever (Japanese river fever). (**a**) Vector: *Trombicula akamushi*, *T. delinensis* (saliva!) (Magnification about 6:1). (**b**) The adult mite (this does not transmit the disease; it does not feed on blood). (**c**) The larva of the mite as the vector to the mouse and as a source of the infection (transovarian infection of the larva). (**d**) The mouse as a reservoir of the causative organism. **Infections series**: rodents–mite larva–imago of the mite–mite larva–man. (**D**) ***Rickettsia rickettsii* Wolbach 1919**. The cause of the Rocky Mountain petechial fever ("Rocky Mountain spotted fever"). (**a**) Vectors: *Dermacentor andersoni*; and also ticks of the genera *Rhipicephalus*, *Amblyomma* and *Haemaphysalis* (saliva!). **Infection series**: Ticks with generative (transovarian) transmission of the causative organism to the next generation of ticks (reservoir of the causative organism) and to man and also the dog (**b**). (**E**) ***Rickettsia conori* Brumpt 1932**. The cause of African tick bite fever ("Fièvre boutoneuse"). Vector: Ticks of the genera *Dermacentor*, *Amblyomma* and *Rhipicephalus*. Dogs and ticks as reservoirs of the causative organism and as vectors. (**a1**) *Rhipicephalus sanguineus.* (**a2**) *Amblyomma hebraeum*, male and female. (**a3**) *A. hebraeum*, engorged female laying eggs: beside it the outline of a fasting female and some larvae (6-legged) and nymphs (8-legged). (**a4**) *Amblyomma pomposum*. (**b**) The dog as the reservoir of the causative organism or as host for the ticks. Infection series: Rodents and dogs–ticks–man. (**I**) *Rickettsia prowazekii*, section through the intestine of the louse. (**II**) *Rickettsia mooseri*, epithelial cell of a mouse

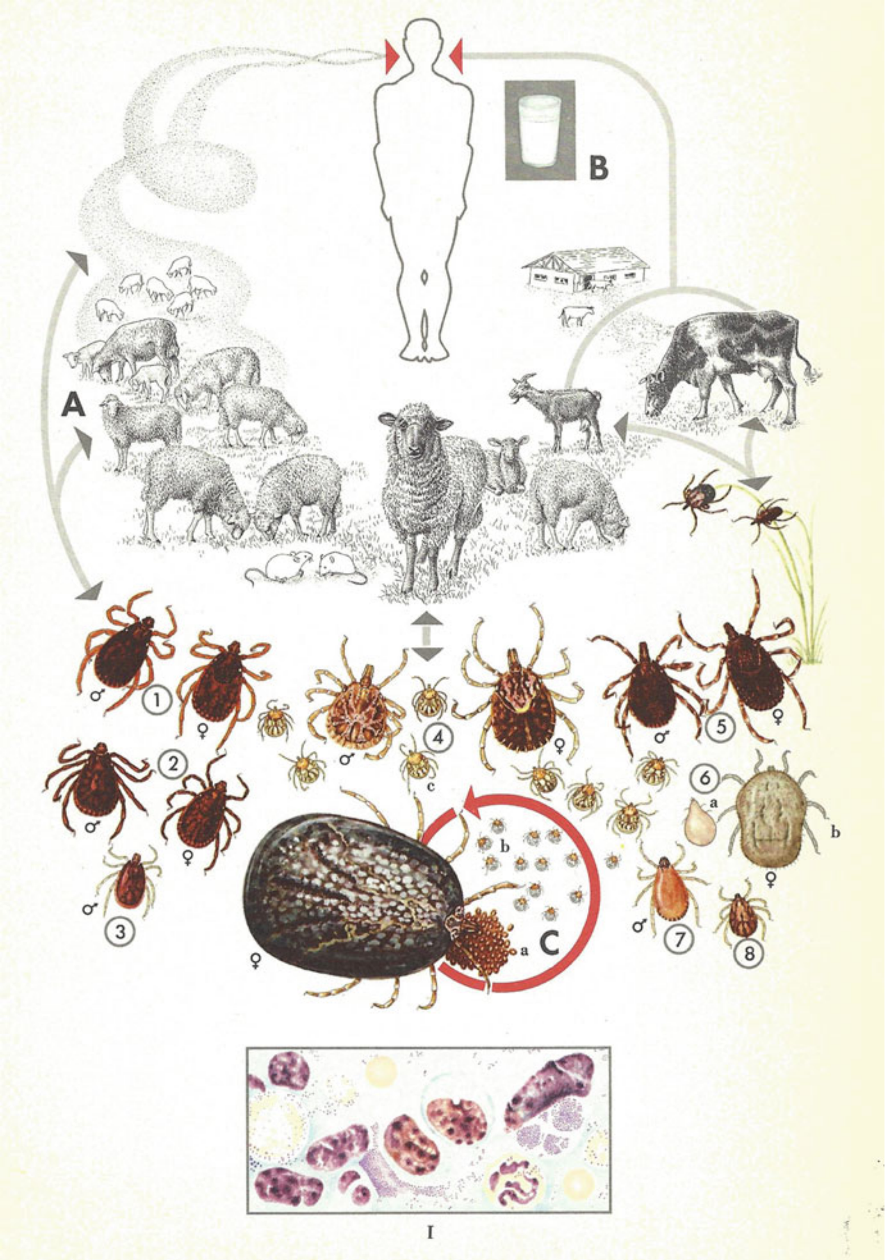

Fig. 5.20 Diagrammatic representation of the transmission of Q fever. **Epidemiology of Q Fever**: Man infects himself. (**A**) By the inhalation of air containing the causative organism derived from sheep, goats, cattle and rodents (aerogeneous mode of infection), for example, during lambing; (**B**) by the consumption of milk and milk products in which there is a latent contamination derived from cattle and goats. (**C**) Numerous species of ticks can carry a latent infection with *Coxiella burneti*; these ticks are the essential reservoir host, because transovarian transmission of the causative organism from one generation of ticks to another can occur. (**1**) *Rhipicephalus evertsi*

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◄

Fig. 5.20 (continued) ♂ and♀. (**2**) *Rh. bursa* ♂ and♀. (**3**) *Ixodes ricinus* ♂. (**4a**) Egg mass of *Amblyomma cajennense*. (**b**) Newly emerged larvae. (**c**) Young nymphs with the sexually mature male and female. (**5**) *Hyalomma transiens* ♂ and♀. (**6**) *Otobius megnini*. (**a**) Larva, (**b**) female. (**7**) *Haemaphysalis* ♂. (**8**) *Boophilus microplus* ♂. Below: (**I**) *Coxiella burneti*, spleen smear from an infected hamster; Giemsa stain

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5.4 Mites

This special group of arthropods comprises a large spectrum of species; however, only a few groups are of medical importance. Due to their rather small body size and their often only short stay on humans and animals, it is rather difficult to diagnose their presence in a dwelling and thus to avoid repeated attacks. Thus, in the following chapter only some important and more common groups are selected.

5.4.1 Chicken Mites (Dermanyssidae)

Dermanyssus gallinae

1. **Name**: Greek: *derma* = skin; *nyssein* = biting. Latin: *gallina* = female chicken; *gallus* = cock; English: Red poultry mite, red chicken mite.
2. **Geographic distribution/epidemiology**: Worldwide.
3. **Biology, morphology**: This bloodsucking parasite is worldwide very common especially in rearing facilities of birds, but also among a very broad spectrum of wild living birds, which introduce them into the nearness of humans which are also attacked. The unfed whitish appearing females measure only 0.7–1 mm in length and 0.4 mm in width, but become much larger after a blood meal (Fig. 5.21). The males measure only 0.6 × 0.3 mm in length. The females are equipped with long cheliceres, which are clutched together and thus become very useful for their sucking activity, while the males possess scissor-like cheliceres. The cuticle of their body shows many folds and is rather smooth so that it may become stretched during blood feeding, thus allowing to ingest huge amounts of blood. Then the mites appear reddish (Fig. 5.21). The eggs measure about 400 × 260 µm and thus are rather large compared to the body size and are deponed hidden but always in the nearness of their hosts. Females lay after blood meals 4–8 eggs—in total about 40. The larva hatches from the egg, grows up

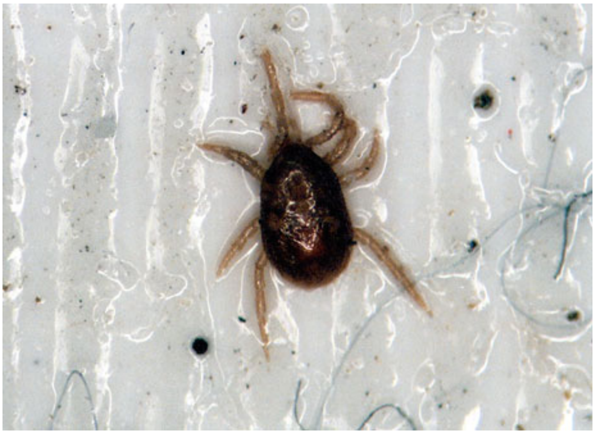

Fig. 5.21 Microscopical photo of a fully sucked chicken mite (*Dermanyssus gallinae*)

without blood sucking, moults to become the **protonymph**, which sucks blood, and moults into the **deutonymph**, which again sucks blood and develops after another moult into the adult male or female stage, which both suck blood. Blood sucking occurs mainly during the night and takes ½ up to 1 ½ h. Under temperature conditions of 20–25 °C, the development of one generation takes 7–12 days, so that the populations inside a chicken stable may reach extreme dimensions in very short periods. These mites may survive 5–9 months without feeding. Thus, the stables must be intensively cleaned after chickens have been removed. This mite may also enter human dwellings, if specimens drop down from wild birds at the windowsill. The total lifespan of an individual female mite is about 5 months (under good feeding conditions).

Humans are attacked when working in poultry stables or even in their dwelling, if mites have entered from windowsills or have been brought into dwelling when keeping birds inside. The mites attack also pet animals like dogs, cats and rabbits when kept in homes.

4. **Symptoms due to bites**: The bites of the nymphs and adult mites of this species are painful and induce strong itching especially when bites occur in large numbers. Bites are seen mainly at the legs, along the neck and throat, on the breast and around the belly. The bites lead to the formation of small papulae and lymph filled small vesicles. In bird stables occur high-grade losses due to the death of the birds, reduced body weight of survivors and due to reduced egg laying.
5. **Transmission of agents of disease**: In the case of humans, no agents of disease are transmitted, while in birds the agents of the so-called chicken plague may be transmitted among other agents of disease.
6. **Control methods**: With respect to establish control measurement, it must be considered that these mites are active at night and suck only for a short while on the host's body. Thus, in stables potential hiding places of mites have to be treated by intensive spraying of chemical insecticides or by plant-derived ones such as MiteStop®. In addition also the infested chickens must be treated—especially when staying permanently in darkened stables. All these treatments should be repeated and intensively done in empty stables before new birds are placed herein.

Further Reading

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5.4.2 Rat Mites (Liponyssidae) and Related Species

A. ***Ornithonyssus* (syn. *Liponyssus, Bdellonyssus*) *bacoti***

1. **Name**: Greek: *ornis, ornithos* = bird; *nyssein* = biting; *bdella* = leach; *lipos* = fat. English: Tropical rat mite.
2. **Geographic distribution/epidemiology**: The tropical rat mite is worldwide distributed and is occasionally introduced in human dwellings.
3. **Bite reactions**: These mites suck during daytime; their bites are painful and lead to intensively itching papulae, which reach diameters of up to 2 cm.
4. **Transmission of agents of disease**: In some southern states of the USA and in Chile, it was found that *Ornithonyssus bacoti* harbours the agents of the marine spotted fever (belonging to the *Rickettsia* group). This mite is used in laboratories to transmit the rat filarial worm *Litomosoides carinii*.
5. **Control**: Spraying of dwelling and animal cages with MiteStop®, which can be used in a 1:50 water dilution (and may also be sprayed on infested animals).

Further Reading

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B. ***Liponyssoides* (syn. *Allodermanyssus*) *sanguineus***

This species (also called house mouse mite) looks very similar to *D. gallinae* and is found in nests of mice, rats and other rodents in Europe, Africa, Asia and North America. From there they may attack also humans and induce skin irritation and itching. **Attention**: They are able to transmit *Rickettsia akari*—the agent of the so-called rickettsial pox disease.

C. ***Ornithonyssus* (syn. *Bdellonyssus*) *sylviarum* (Nordic fowl mite)**

1. **Name**: Greek: *ornithos* = belonging to birds. Latin: *sylva, silva* = forest. English: Northern fowl mite.
2. **Biology**: This mite, which measures as female 0.6–0.8 × 0.3–0.5 mm and about 0.5 × 0.4 mm as male, attacks in regions with moderate climates many free-living birds but also farmed bird species (Fig. 5.22). In contrast to *Dermanyssus gallinae*, the whole development occurs on the body of their hosts and can be done within 5–7 days running via a larva and two nymph stages. These mites can only starve for 3 weeks. Humans are also attacked. The shield of the females covers two-thirds of the backside and its cheliceres are long and show a scissor-like structure at their terminal ends.
3. **Bite reactions, agents of disease, etc.**: See *Dermanyssus gallinae*.

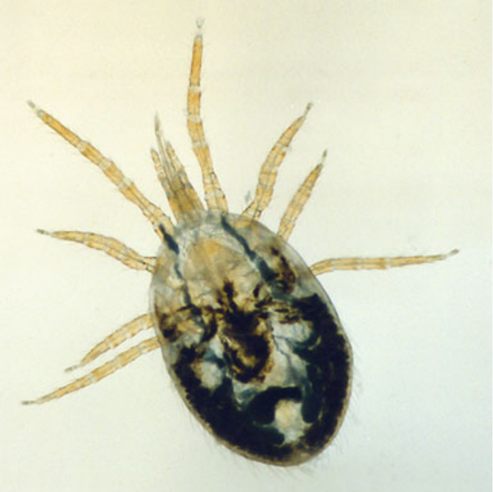

Fig. 5.22 Microscopic photo of the northern fowl mite filled with blood. This species stays all the time on its once entered host

4. **Control**: Can be done by submersion of chickens into a 1:40 diluted solution of MiteStop®.

Further Reading

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D. *Ophionyssus natricis*

1. **Name**: Greek: *ophis* = snake. English: Snake or reptile mite.
2. **Biology**: This snake mite sucks blood on snakes, but occasionally also on humans that keep snakes, lizards, etc.
3. **Treatment**: Mites on snakes may be killed by Acarol® (Fasera, Fa. Alpha-Biocare, Düsseldorf).

Further Reading

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5.4.3 Trombiculidae (Chigger Mites)

1. **Name**: Greek: *thrombos* = clod, knot; *neos* = new. English: Chigger mites, harvest mites, red bugs.
2. **Biology/morphology**: The larvae of these mites appear intensively red, reach a length of 0.3 mm and have an ovoid, flat body (Fig. 5.23, 5.24). Worldwide about 700 species exist. About 20 of them may attack humans and may induce dermatitis or are able to transmit agents of diseases. For long, these species were known/collected under the genus names *Leptus, Atoma*, etc. However, as soon as the soil-inhabiting adult stages had been discovered renaming was needed. In Europe especially the following species have got importance for humans: *Neotrombicula* (*Trombicula*) *autumnalis, Trombicula toldti* and *Euschöngastia xerothermobia. N. autumnalis* occurs besides in Europe also in East Russia, Turkey, China and regions of North America. The adult stages live and overwinter in the soil and may wander in cases of arid soil, freezing or rain up to a depth of 1 m. They reach a length of up to 2 mm and possess long, whitish feather-like cuticle hair. In Europe, the adult females depone their eggs during the months of May until September onto the soil. Depending on the temperatures, the six-legged larvae hatch rather soon from the eggs. On meadows, in private gardens as well as in public parks they lurk for hosts such as rats, mice, rabbits and other warm-blooded animals inclusive humans, which were attacked in masses. In rather cold countries like Germany, only one generation occurs per year, while in warmer countries several generations may follow each other.

   The compact anterior ends of these larvae are equipped by pairs of sickle-like cheliceres and pedipalps. If these larvae have got contact with a host, they attach themselves at smooth places of the skin and start to suck. In the case of humans, they suck in the regions of the legs but also all over the whole body, whereby the cheliceres were injected into smooth skin regions. The introduced saliva dissolves skin tissue, thus giving rise to a channel-like tube called **stylostome**, which reaches deep into the skin—often until the corium. By the help of this “tube” the mite larvae suck dissolved cell material and lymph fluid, but **never blood**. This process goes on for up to 3–5 days, if they are not disturbed. After sucking they drop down to earth and moult themselves into soil-living nymphs and later to adults (Figs. 5.23, 5.24). The nymphs and adults are no parasites.
3. **Bite reactions**: The injection of the mouthparts is not noted by the hosts, even if there are large numbers of attacking larvae. The introduced saliva, however, initiates itching. The starting point and severity of this so-called **scrub itching** depends on the sensitivity of the host. However, in general this itching is especially intensive about 2–3 days after the infestation and leads to the formation of red **papulae**, which may reach diameters of up to 3 cm (Fig. 5.25). In cases of repeated bites, itching and sensitivity are increased.
4. **Prophylaxis**: Repellents with icaridin, such as Autan® or Viticks®, avoid bites, if they are intensively sprayed on shoes, legs and trousers.

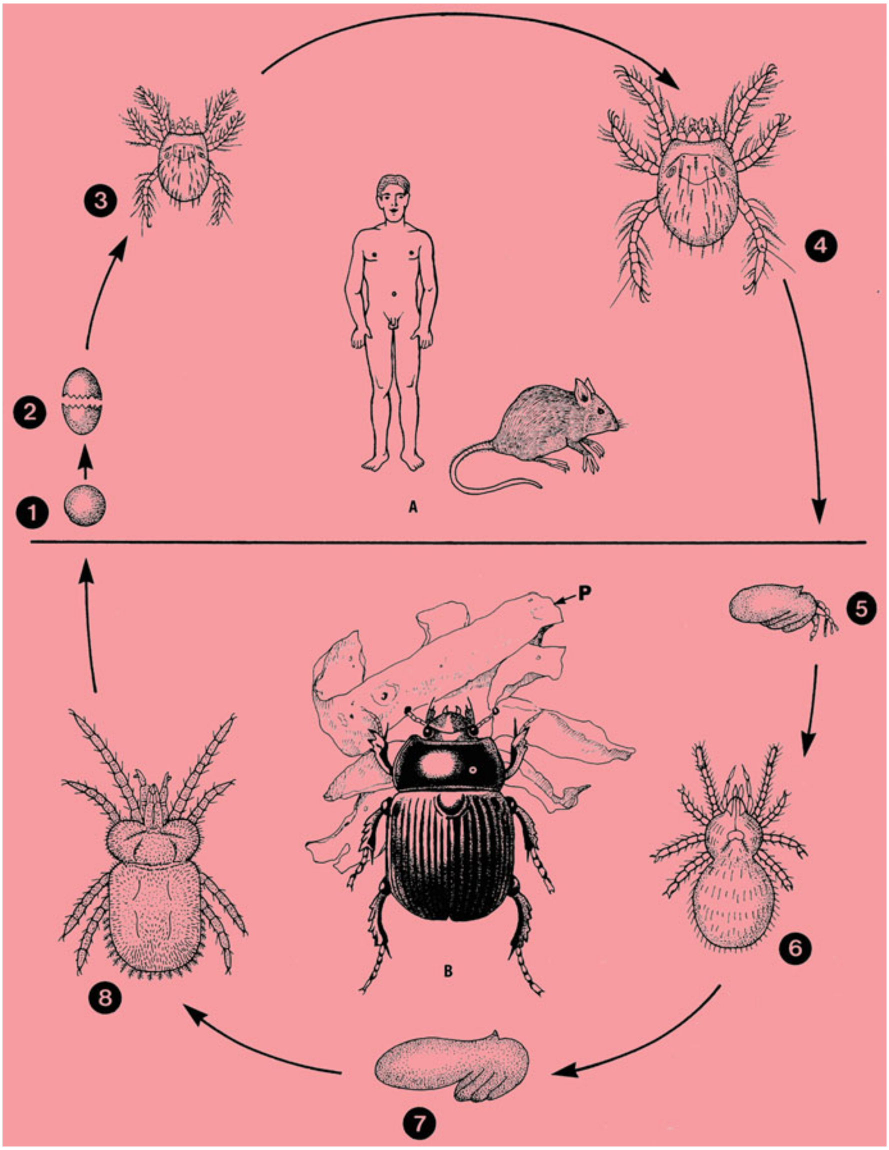


Fig. 5.23 Life cycle of the so-called autumn mites *Neotrombicula autumnalis*. Only larvae attack humans and other hosts. (**1**) Egg. (**2**, **3**) Larva hatches. (**4**) Larva sucks lymph at warm-blooded hosts (**a**). (**5**) After the end of the single sucking period the larva enters the soil and moults to become the **protonymph** stage. (**6**) The motile **deutonymph** is formed by hatch of the protonymph. (**7**) **Tritonymph** staying in the soil. (**8**) After the moult of the tritonymphs the adult male and female reach fertility, come at the surface (e.g. of meadows) and are transported by beetles (**b**) throughout the biotope and/or into store houses

Fig. 5.24 Macro- (**a**) and light microscopic (**b**) photos of the 6-legged larvae of the harvest mite *Neotrombicula autumnalis*

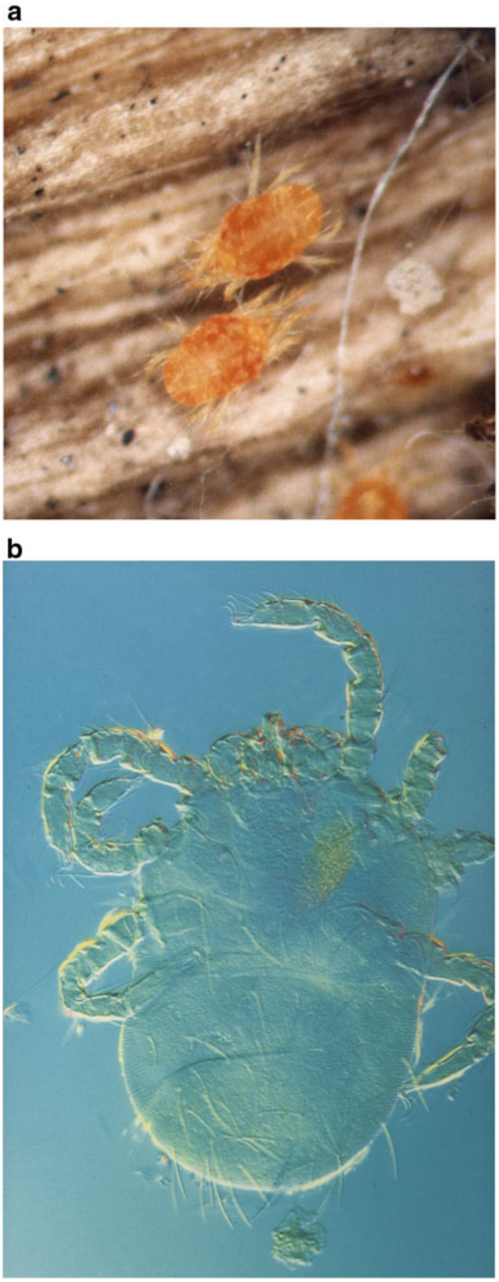
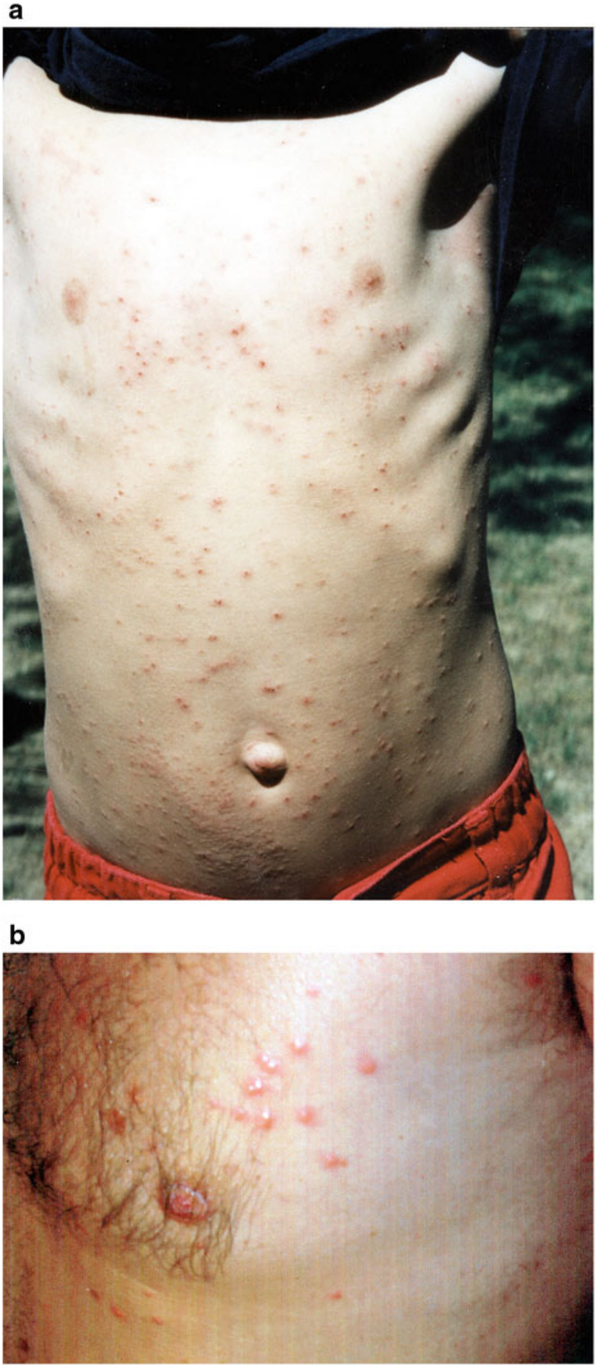


Fig. 5.25 Typical skin reactions after lymph-sucking activity of *Neotrombicula autumnalis*



5. **Symptoms of disease**: The bites themselves lead to severe itching and formation of skin papulae. If agents of disease are transmitted, it takes species-specific incubation periods of up to 14 days until symptoms such as fever, headache and/or exanthemas appear. In cases of bites along the groins painful lymph node swellings occur. **Therapy**: application of doxycycline.
6. **Agents of disease**: The larvae of *Leptotrombidium akamushi* and *L. delicense* transmit the most dangerous mite-transmitted agents of disease (those of the so-called **scrub typhus**) or *Tsutsugamushi* fever (=*Rickettsia tsutsugamushi* (syn. *R. orientalis*). These agents are mainly found in East and Southeast Asia, India, New Guinea, North Australia and on islands of the Indian and Pacific oceans. The larvae ingest these agents and transfer them to the nymphs and adults. The adult females transmit the rickettsiales into the eggs, so that the hatching larvae can transmit them to their hosts. Due to antigen variations in the case of *R. tsutsugamushi*, very often recidives occur or even new infections become possible. The lethality rate is high; in untreated cases it may reach 5–20 % depending of the age of the patients.

   Similar symptoms occur due to bites of other species of the so-called trombidiforme mites, which live in natural products such as cereals and hay of straw. An example is the so-called "ball-belly mite" (***Pyemotes*** (***Pediculoides***) ***ventricosus***) which primarily feeds on moths, beetles and wasps but also attacks humans working with the above-cited products. The grain or hay itch mite ***Pyemotes tritici*** induces strong itching and the appearance of papulae. *Pyemotes* bites lead in general to strongly itching protrusions and blisters. The females of this species are characterized by the fact that they possess a ball-like enlarged hindbody.
7. **Control**: Stored material can be heated up, areas and floors in storage buildings can be sprayed with MiteStop® (Fa. Alpha-Biocare) and persons may use repellents (Autan®, Viticks®).

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5.4.4 Fur Mites (Cheyletiellidae)

1. **Name**: Greek: *cheilos* = lips. English: Fur mites.
2. **Biology/morphology**: Species of the genus *Cheyletiella* parasitize in the fur of cats and dogs. *C. blakei* occurs on cats in Europe, America and Africa, *C. yasguri* is found on dogs and *C. parasitivorax* occurs on rabbits. If dogs

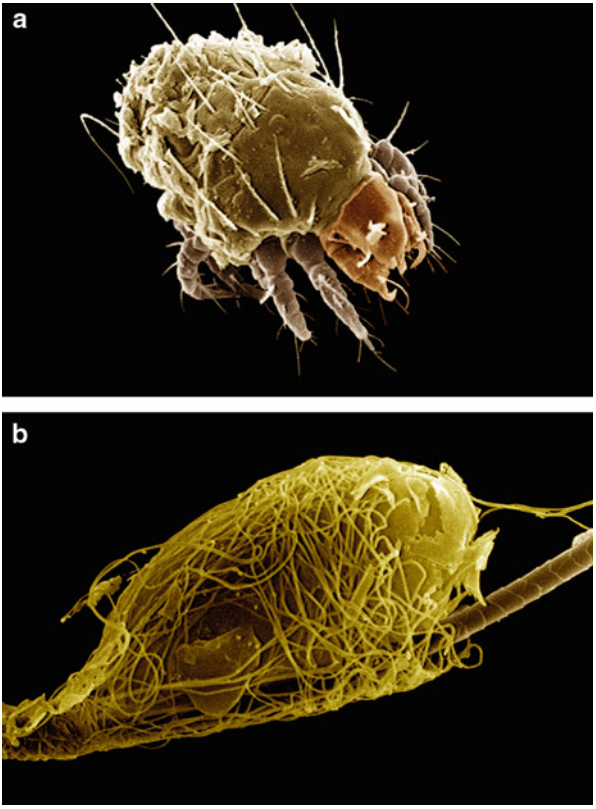

Fig. 5.26 Scanning electron micrograph of stages of *Cheyletiella* sp. (**a**) adult stage; (**b**) egg, which is glued at a hair by the help of fine filaments excreted by the female

and cats get into contact, *C. yasguri* may also be transferred to cats. These mites, however, may also attack humans, if they live together in a household. The *Cheyletiella* species (Fig. 5.26) glue their eggs by the help of fine filaments at the base of the hair of their hosts (Fig. 5.26), so that the hair in the case of mass infection glue together and look whitish. In cats mainly the back region is affected besides the site behind the ears. In dogs also the back is mainly affected, while in the case of rabbits mainly the shoulder region is parasitized. In those humans who have close body contacts with their pet animals, very often regions along the breast and arms show skin alterations such as itching and reddish papulae, which reach diameters of 0.5–1 cm. In general the symptoms disappear as soon as contact with infected pet animals is stopped.

3. **Diagnosis**: The eggs (230 × 100 μm) of the mites and their tiny stages (one larva, two nymphs, male and female) can be microscopically diagnosed by the help of transparent glueing stripes. The adult stages appear ovoid, measure about 200–500 μm in length and are equipped with stiletto-like cheliceres.
4. **Treatment**: Treatment of dogs, cats and rabbits can be done by chemical compounds such as imidacloprid, fipronil and selamectin or by washing them with the human anti-louse shampoo Licener®, too.

Further Reading

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Saevik BK et al (2004) *Cheyletiella* infestation of the dog. J Small Anim Pract 45:495–500.

5.4.5 Scabies Mites (Sarcoptidae)

1. **Name**: Greek: *sarx* = meat; *koptein* = twisted. Latin: *scaber* = rough, not clean. English: Scabies mites.
2. **Geographic distribution/epidemiology**: Worldwide, especially among people in groups of humans who live closely together.
3. **Biology, morphology**: The scabies mites (*Sarcoptes scabiei*) dig up to 1 cm long channels inside the epidermis of humans and many animals (where subspecies/races occur). The nymph and adults are characterized by four pairs of stumpy legs, while the larvae have only three pairs (Figs. 5.27 and 5.28). The adults reach a size of 0.3–0.5 × 0.2 × 0.4 mm, stay on the skin and feed skin particles. There the females become fertilized by the males, which die

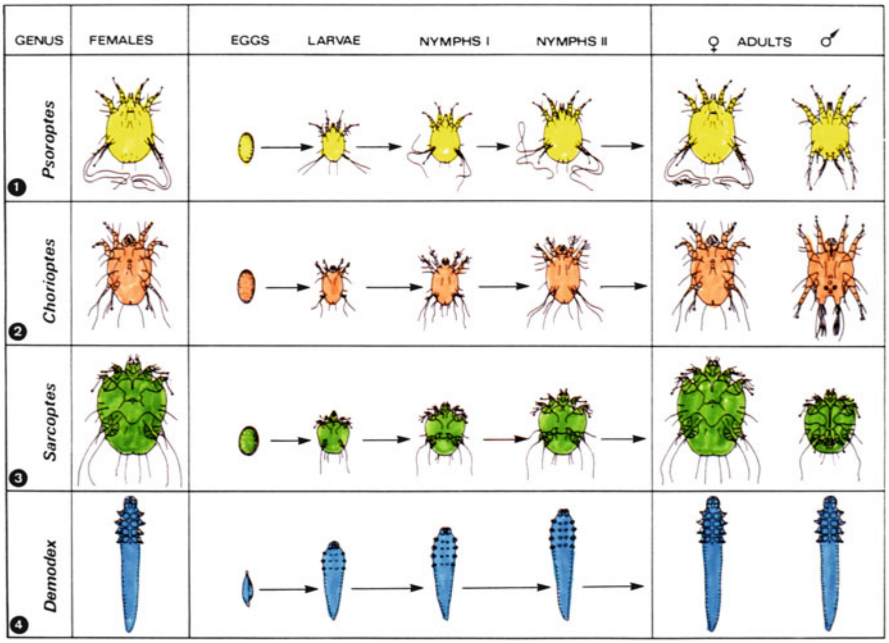

Fig. 5.27 Diagrammatic representation of the stages of important mites

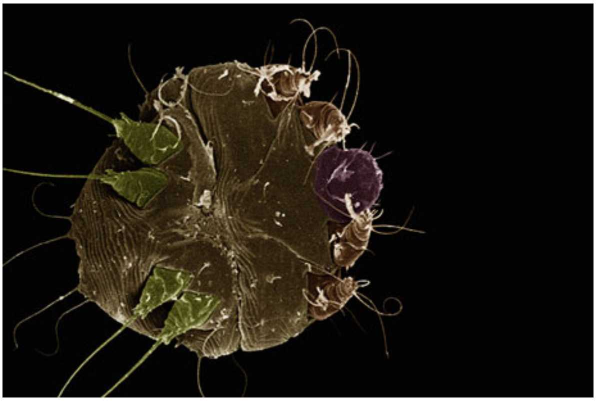

Fig. 5.28 Scanning electron micrograph of the scabies mite (*Sarcoptes scabiei*)

afterwards. Then the females enter the skin by digging a channel, which takes about 30 min. Inside their skin channel the females lay eggs (1–4 daily for up to 4 months) from which the six-legged larva hatches and starts a feeding process to reach the surface. After another moult on the surface, the adult stage is reached and the fertilized females dig a new channel into the epidermis. The development of the larvae and two nymphs inside the skin channels takes 9–10 days for males and 12–15 days for females (they reach the skin surface later than the males). The infection of new hosts occurs, when a fertilized female wanders during skin-to-skin contact from one person to another one. There exist skin spots, which are especially often infested (Fig. 5.29).

4. **Symptoms of the disease**: Infections mainly start by inflammation reactions between the fingers, in the region of the sexual organs or along the groins, from where spreading may all over the body and may even reach the head skin (Fig. 5.30a–c). In the case of immuno-suppressive persons, spreading may be especially intensive leading to large regions of destroyed, suppurating remnants of the epidermis (Fig. 5.30a). The final appearance of such crusts or scabs is described as **Norwegian scabies**. Especially in the evening and night hours scabies is accompanied by intense itching.

   The following stages can be differentiated along human skin after an infection by scabies mites.

   (a) **Mite channels**: The mostly only 1–4 mm long channels end in a terminal slightly enlarged bladder that surrounds the fertilized female excreting the eggs. These channels appear reddish to brownish and may contain blood after intensive scratching.

   (b) **Secondary exanthema**: This sign appears mostly as hypersensitivity reaction on antigenic material excreted by the skin-boring females. Eczemas are also often seen during this phase of infection.

   (c) **Hyperkeratotic skin crusts**: This symptom is especially often found in immunosuppressed adult humans as well as in children along the whole body and occurs also in the face. If the brownish crusts reach ½ cm in diameter, the symptom is described as **Norwegian scabies** (*Scabies norwegica*) (Fig. 5.30a).

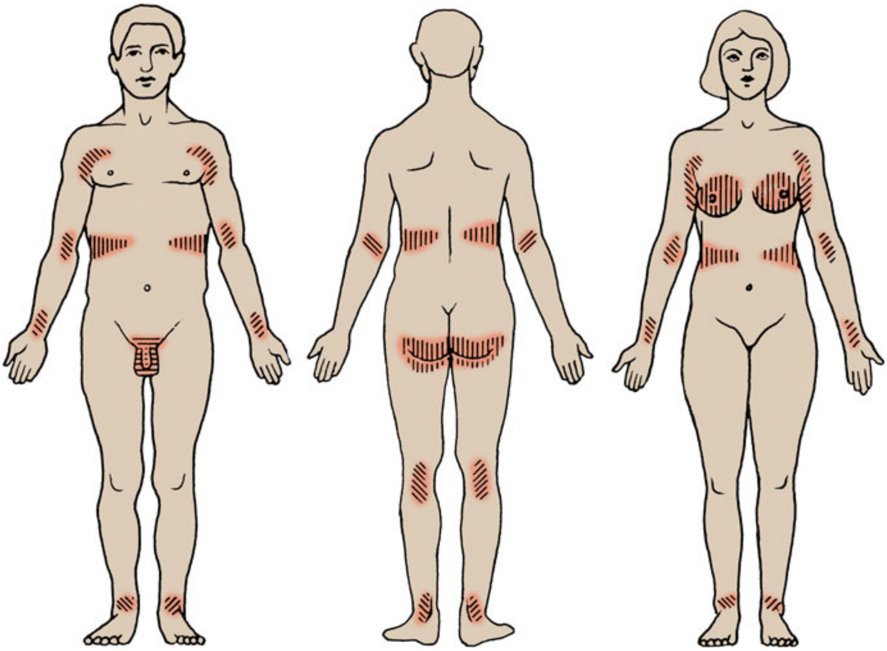

Fig. 5.29 Skin sites that are often attacked by scabies mites

(d) **Superinfection by bacteria** of the skin channels is often induced by feeding females. These channels show different aspects depending on the bacterial species.

5. **Diagnosis**:
   - **Skin inspection**: Increased pruritus, fine papulae eventually combined with exanthemas, appearance of short inflamed channels inside the epidermis; females might be obtained by the use of fine needles for skin perforation.
   - **Skin scrapes**: By the help of a scalpel, portions of an inflamed skin region were obtained, placed for 5–30 min (depending on the thickness of the probe) into a 10 % potash alkaline solution and afterwards checked by the help of a light microscope. The typical mites, remnants of them or their eggs can be easily seen since alkaline solution dissolves the human tissues but not the chitin surrounding mites and their eggs.
6. **Pathway of infection**: Body contact with skin of infected persons or animals. Fertilized females (=telonymphs) migrate to the new host, enter the skin and start egg production inside their skin channel (1–4 eggs per day).
7. **Prophylaxis**: Avoidance of contact with the skin of infected persons or animals and avoidance of common use of clothing or bed sheets with foreign people.
8. **Incubation period**: Lately 14 days after an infection the first skin symptoms are noted.
9. **Prepatent period**: First larvae occur about 15 days after a fertilized female has entered a new host.

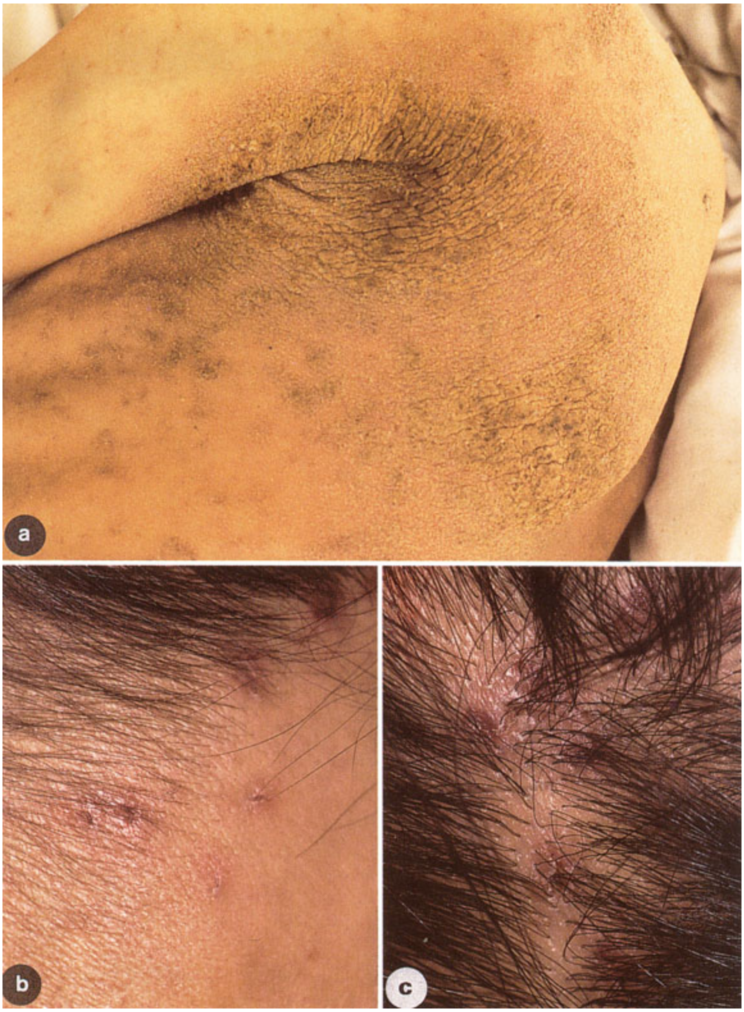

Fig. 5.30 Scabies symptoms: (**a**) Scabies norvegica in a HIV patient. The infected, crust-rich regions contain huge amounts of mites. (**b**, **c**) Entrance sites of mites in hair regions

10. **Patency**: Females live for about 2–3 months. However, due to permanent self-infections, humans may suffer for years from scabies.
11. **Therapy**: Officially registered products containing permethrin, crotamiton or benzylbenzoate are very toxic and should not be used. In addition resistances against these compounds have been developed by the scabies mites. Today the drug of choice is **ivermectin**, which is registered in France for humans, e.g., as **Stromectol® and in Germany as Scabioral®** and thus can be ordered by physicians via the International Pharmacy system. As a dosis is recommended 1x orally 200 mg ivermection/kg body weight. After 2 weeks

has to be decided, whether a secon dosis is needed (e.g. in cases of new lesions). This compound is used since years without any side effects in human cases. Also in millions of cattle and pigs, it did not introduce any problematic symptoms. Reduction of itching and other skin reactions occur within 1–2 days and the skin efflorescences disappear within 10–14 days.

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Rider SD et al (2015) Draft genome of the scabies mite. Parasit Vectors 8:585.

Zahler M et al (1999) Molecular analyses suggest monospecifity of the genus *Sarcoptes*. Int J Parasitol 29:759–766.

5.4.6 Follicle Mites (Demodicidae)

1. **Name**: Greek: *edemas* = body; *dex* = stretched. Latin: *folliculus* = small bladder; *brevis* = short.
2. **Geographic distribution/epidemiology**: Worldwide, most common are transmissions between mother and child; practically all humans bear such mites—mostly without knowledge.
3. **Biology, morphology**: The follicle mite (*D. folliculorum*) and the mites of the sebaceous glands (*D. brevis*) measure as adults 0.3–0.4 mm and 0.25 mm, respectively, in length and are cigar-like shaped (Figs. 5.27 and 5.31). Their legs are very short. The life cycle, which starts from 70–90 μm × 20–25 μ sized eggs, runs via 1–2 larval stages and two nymphs until the females and males occur, is finished within 2–3 weeks. The males die after 3–5 days, while the females enter the follicle of the hair, where they depone about 20 eggs before they die, too. The copulation has been proceeded on the surface of the skin. During this phase, the transmission to other humans may occur during body contacts.

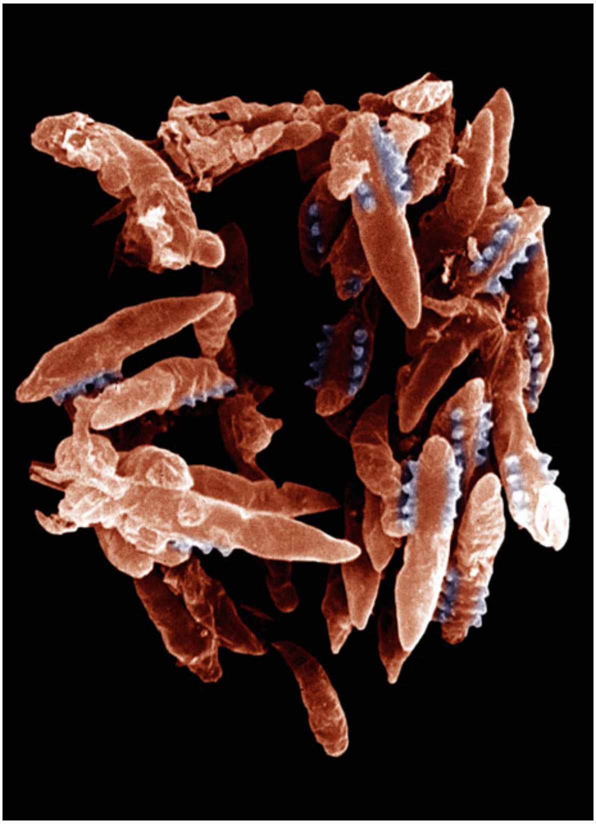

Fig. 5.31 Scanning electron micrograph of numerous adult stages of *Demodex folliculorum* after digestion of squeezed-out sebaceous skin material

4. **Symptoms of the disease**: Although the infection rates of humans increase up to 100 % during lifespan and up to 1000 mites may be present at the same time, clinical symptoms are rarely seen in healthy persons. However, especially immunosuppressed people may show keratinization besides rosacea, areata-like alopecia, pyoderma, lupus miliaris, blepharitis, perioral dermatitis and/or micropapular lesions.
5. **Diagnosis**: When squeezing the skin in affected symptomatic regions (especially that of the noso-labial zone), the obtained sebaceous compounds may contain the cigar-shaped mites which can be made visible (for light microscopy) by mixing the material with a droplet of concentrated lactase.
6. **Pathway of infection**: Intense skin-to-skin contact—especially between mothers and their baby.
7. **Prophylaxis**: Regular hair and body cleaning.
8. **Incubation period**: About 2 weeks, if at all symptoms occur.
9. **Prepatent period**: 2 weeks.
10. **Patency**: Years due to repeated self-infections.
11. **Therapy**: See scabies mites.

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5.4.7 House Dust Mites (Tyroglyphidae)

1. **Name**: Greek: *tyros* = cheese; *glyphein* = invade, enter.
2. **Biology, morphology**: The family Tyroglyphidae comprises 5 genera with a total of 13 species. Three species of the genus *Dermatophagoides* (Figs. 5.29, 5.32 and 5.33) are worldwide distributed. With respect to human disease, the following four species are most important:

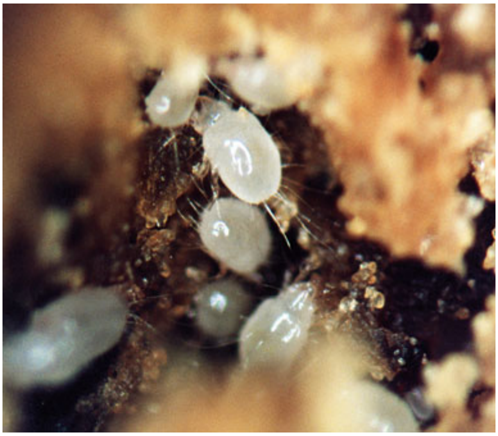

Fig. 5.32 Light micrograph of adult house dust mites (*Dermatophagoides pteronyssinus*)

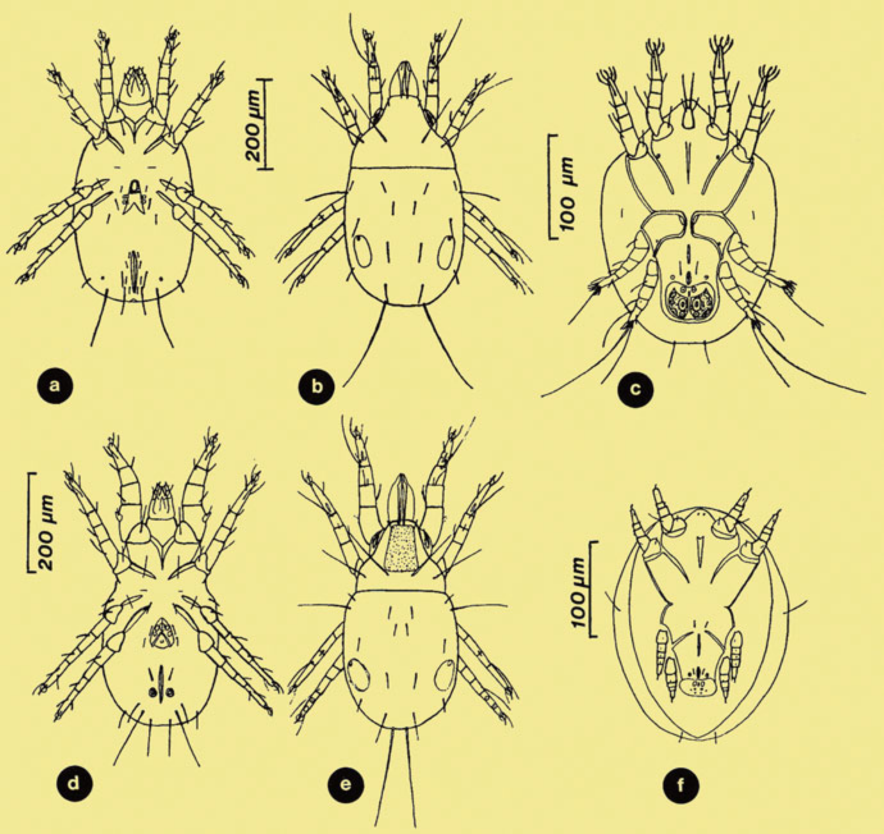

Fig. 5.33 Mite species inducing symptoms of allergy. (**a–c**) Developmental stages of *Acarus siro* (*Tyroglyphus farinae*)—agent of the so-called baker's scabies. Especially the long bristles may induce symptoms of disease. (**a**) Female, ventral side; (**b**) female, dorsal aspect; (**c**) migrating nymph; (**d**) male, ventral side; (**e**) male, dorsal aspect; (**f**) permanent nymph

- ***Dermatophagoides pteronyssinus*** (Fig. 5.32),
- ***Dermatophagoides farinae***,
- ***Euroglyphus maynei***,
- ***Acarus siro* (*Tyroglyphus farinae*)**.

These mites measure in length about 300–700 µm and are characterized by long hair (Figs. 5.32, 5.33) and are found in organic substances such as house dust, on seeds and skin scales.

3. **Symptoms of the disease**: Healthy persons show mostly low-grade symptoms—if at all. Young children, old or immune-suppressed people, however, may suffer from several intense allergic reactions by inhaling fecal dusts, portions of dead mites, etc. Especially house dust mites may induce symptoms of asthma, conjunctivitis, rhinitis, etc.

4. **Diagnosis**: Best and quickest information on the presence of mites in a dwelling are obtained by so-called “mites-feces tests” offered by several companies worldwide. They show quickly the presence of no, slight or huge amounts of mite feces in house dust. Other tests using cleaned dust allergens, which are injected into human skin, determine whether an allergy is present or not.
5. **Therapy**: Treatment is needed in cases of severe allergic reactions. Immune therapies reduce the intensity of the allergic symptoms close to zero.
6. **Control**: Treat contaminated floors with products which dry the larval and adult mites (Tresan®, MiteStop®).

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5.5 Insects (Insecta, Hexapoda)

The class of Insecta is the largest group of animals on earth with respect to the number of species and the number of individuals belonging to a single species. The scientific system of the Insecta includes two main groups:

- **Apterygota**: Rather simply organized species without wings and a low-grade body organization.
- **Pterygota**: From Greek: *pteron* = wing. These so-called higher insects include winged and wingless genera with a complex life cycle. In the group of wingless species, the formerly existing wings are completely reduced or still visible as remnants. All parasitic species belong to this group.

Only parasites of humans are included in the shortened extract of the Zoological System listed below:

System
Phylum: ARTHROPODA (selection).
Subphylum: Tracheata.
  Class: Insecta (Hexapoda).
  Subclass: Apterygota (without wings).
  Subclass: Pterygota (winged).
    Order: Phthiraptera (lice).
      Suborder: Anoplura—sucking lice.
      Suborder: Mallophaga—biting lice.
    Order: Rhynchota (bugs).
      Family: Reduviidae—raptor bugs.
      Family: Cimicidae—bedbugs.
    Order: Diptera (specimens with one pair of wings and one pair of halteres).
      Suborder: Nematocera (specimens with long antennae).
        Family: Phlebotomidae (sandflies).
        Family: Culicidae (mosquitoes).
        Family: Ceratopogonidae (midges).
        Family: Simuliidae (blackflies).
      Suborder: Brachycera (flies with short antennae).
        Family: Tabanidae (tabanids).
      Suborder: Cyclorrhapha (flies with circularly seamed eggs).
        Family: Muscidae (house flies).
        Family: Glossinidae (tsetse flies).
        Family: Sarcophagidae (flesh flies).
        Family: Gasterophilidae (stomach flies).
        Family: Oestridae (bot flies).
        Family: Hippoboscidae (louse flies).
    Order: Siphonaptera—(fleas).

Insects as ectoparasites may serve as:

- **Intermediate hosts** for important parasites of humans and his farm or pet animals (such as protozoans, tapeworms, trematodes, etc.),
- **Vectors** for important agents of diseases such as rickettsiae, bacteria, viruses and parasites,
- **Mechanical transmitters** of cyst stages of protozoans, eggs of all worm groups, fungi, bacteria and viruses.

Insects as endoparasites are less common than ectoparasites, but nevertheless they may introduce severe diseases:

- **Myiasis** (fly larvae inside skin, eyes, genital openings, etc.),
- **Tungiasis** by sand fleas (*Tunga* species) entering the skin.

The morphology of the adult stages of higher insects (Pterygtota = winged insects) shows many adaptations to their different lifestyles, but also many common features:

1. Insects appear as males and females and have a dimorphic appearance.
2. Their segmented body comprises head (**caput**), breast (**thorax**) and torso/trunk (**abdomen**).
3. The body is covered by a chitinous **exoskeleton** which is moulted while growing.
4. The original segments of the head are melted to form a capsule, which is provided with a pair of **compound eyes**, one pair of segmented **antennae** and three pairs of ventrally arranged mouthparts (**maxilla 1 and 2; mandibles**). However, mouthparts and eyes may be reduced within several species.
5. Each of the segments of the thorax (**pro-, meso-, metathorax**) bears ventrally a pair of legs (this feature led to the group name: **hexapoda**).
6. The legs consist of five segments: **coxa, trochanter, femur, tibia and tarsus**. The tarsus is provided with species-specific claws or other hold-fast systems. Due to this appearance of the legs, this group is characterized by the Greek term **arthropoda** = animals with segmented legs.
7. Many species possess a pair of functional **wings** plus a pair of reduced ones (halteres) or remnants of them at the dorsal side of the meso- and metathorax. The appearance of the wings is species specific and can be used for species determination. Some groups (e.g. fleas, bedbugs) have totally reduced their wings.
8. The segments of the abdomen do not show leg-like structures, but may be provided with protrusions that are used during copulation or during care for progeny. Inside the abdomen, the sexual organs are located, as well as the intestine, accessory glands and the excretory system (=Malpighian tubules).
9. Breathing (=uptake of oxygen) of insects is done by the help of a tubular, chitinous tracheal system, which starts at the surface of each segment by an opening (**stigma**) and may reach practically each body cell.
10. The tube-like heart is situated at the dorsal side and pumps via its anterior and posterior opening the body fluid (=haemolymph) throughout the body.
11. The nerve system is located ventrally starting at the two “cerebral” ganglia inside the head and stretches until the body end.
12. The anterior and central region of the intestine contains a sack-like so-called **peritrophic membrane** which consists of chitin filaments and thus protects the intestinal cells. Furthermore, the food becomes filtered by this layer, so that many parasites and agents of diseases are kept away from the smooth intestinal layer. However, many parasites (e.g. trypanosomes, filarial worms) have developed means to pass this barrier.

13. Insects with wings are named **pterygotes**, while wingless ones are called **apterygotes**.
14. The primary pterygote insects are differentiated according to their life cycle into two groups:
    – **Hemimetabolous insects** and
    – **Holometabolous insects**.

Among the **hemimetabolous insects** the individual development occurs step by step via moults of the larval stages, which look already very similar to the adults (e.g. this is the case in lice and bugs). The **holometabolous insects**, however, develop **larvae**, which are wingless and look completely different to the adult stages. After several species-specific larval moults, a **pupa stage** is formed. During this phase, the development (=transformation of the larval body into the adult one) proceeds inside of a more or less stable pupal cover. In some other species, motile pupae occur (e.g. in mosquitoes).

5.5.1 Fleas (Siphonaptera)

1. **Name**: The source of the English name comes from the medieval term "fliehan" = to flee; Greek: *syphon* = tube; *pteron* = wing; *aphanes* = hidden, small. French: flea = *puce*.
2. **Biology, morphology**: The body of the fleas is laterally depressed which makes it easier to pass through the hair of the hosts (Figs. 5.34, 5.35, 5.36, 5.37 and 5.38). By the help of their long legs, fleas are able to jump up to 35 cm wide and high, so that they can reach hosts, which pass by. All flea species are wingless and their laterally compressed body has a colour that reaches from light brown to nearly black. Their head is rather small and bears a pair of short, retractable antennae. The arrangement of the rather scarce bristle-like hair is used to differentiate among species. The mouthparts are also rather small, so that during

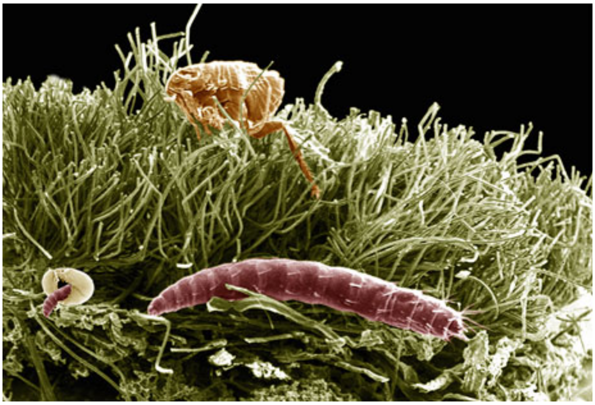


Fig. 5.34 *Pulex irritans*. Scanning electron micrograph showing an adult flea, a hatching larva and a large last-stage larva

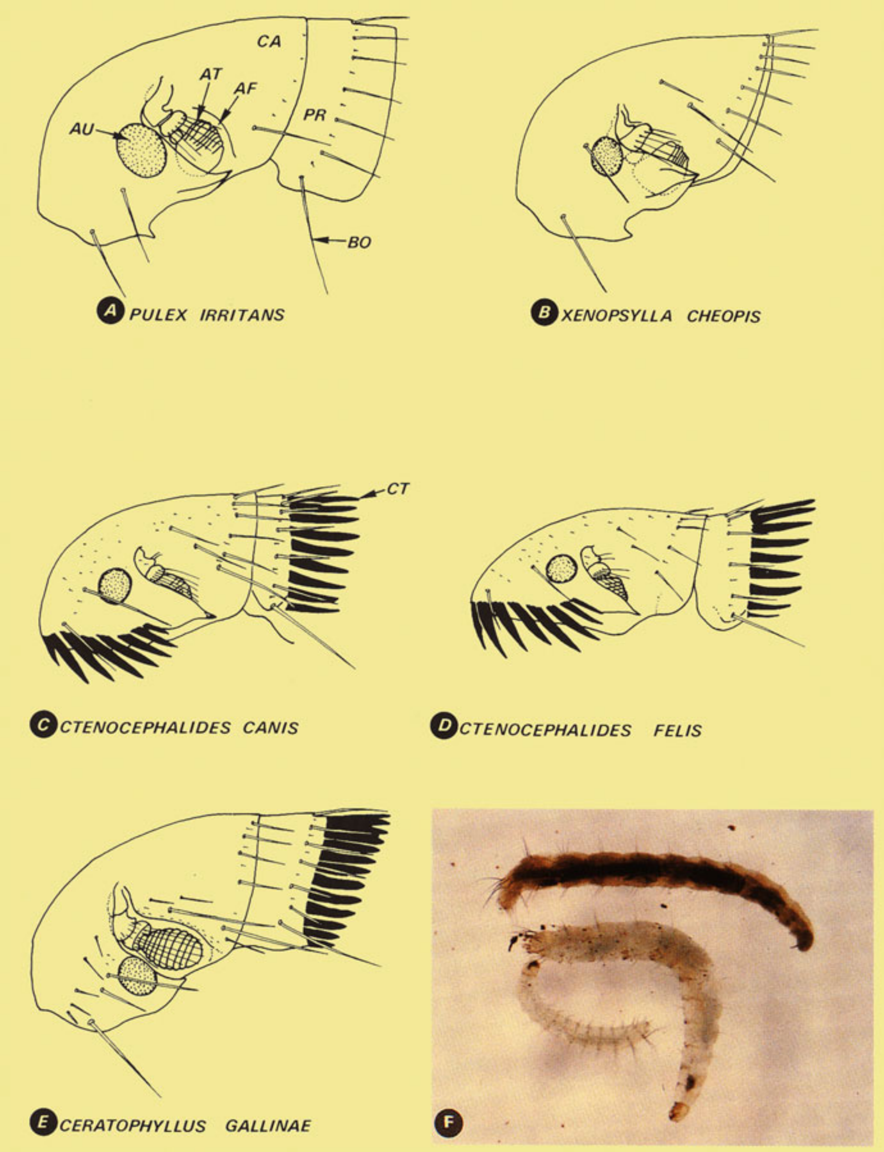

CA
AT
AF
AU
PR
BO
A PULEX IRRITANS
B XENOPSYLLA CHEOPIS
CT
C CTENOCEPHALIDES CANIS
D CTENOCEPHALIDES FELIS
E CERATOPHYLLUS GALLINAE
F

Fig. 5.35 Diagrammatic representation of the head region of fleas and light micrograph of larvae (F). *AT* groove of antennae; *AT* antennae; *AU* ommatidium = eye; *B* bristles; *CA* head; *CT* combs; *PR* pronotum

blood sucking only the epipharynx and the laciniae enter into the skin. The short, retractable antennae consist of two basal segments and a terminal portion which comprises several closely arranged, flattened segments. The middle and terminal pair of the legs is used for jumping and possesses an elongated coxa and

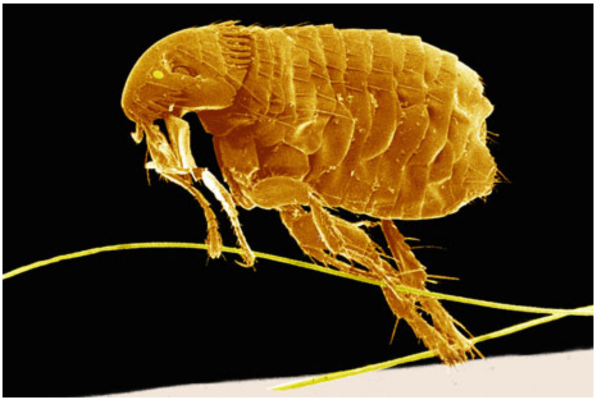


Fig. 5.36 Scanning electron micrograph of the lateral aspect of the cat flea *Ctenocephalides felis*

considerably thickened femur. Their tarsus consists of five segments. The terminal one is provided with rather strong claws which help to stay inside the fur or feathers of their hosts. The rather large abdomen of the fleas is provided with a so-called **pygidial plate** which is equipped with sense cells (**trichobothria**), which help to perceive air streams and odours of arriving hosts.

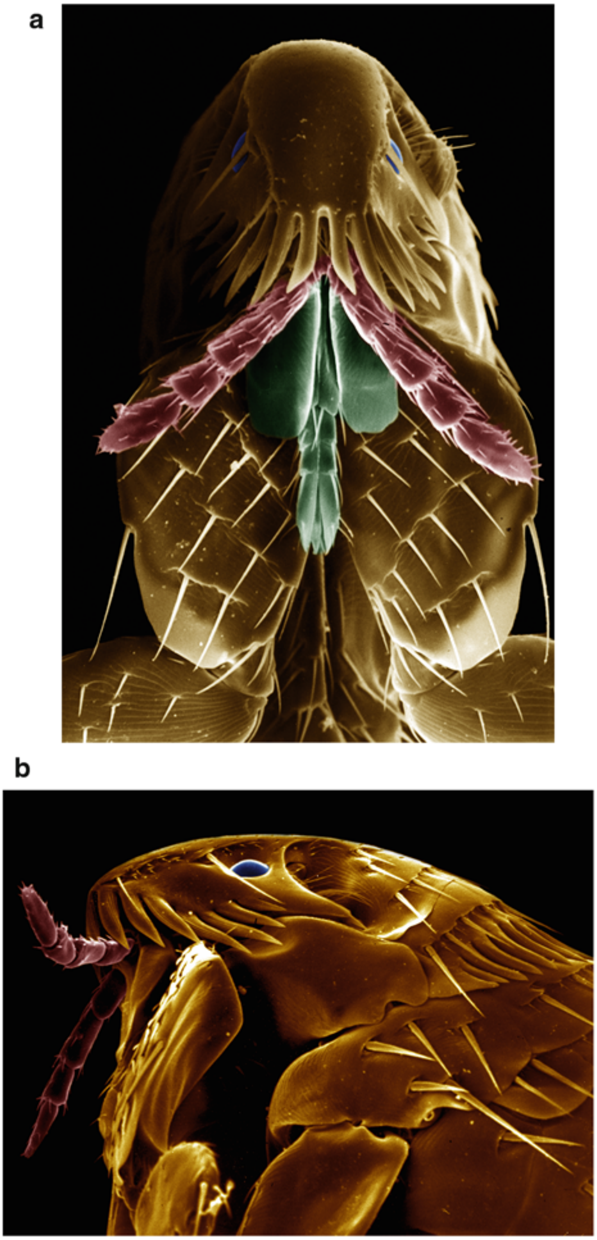
Both sexes of the fleas suck blood (6 % at birds, 94 % at mammalians). In general, fleas are rather host specific; however, after long starving periods they attack also hosts, which normally do not belong to their host spectrum. According to Peus (1972), the hosts are described as "**main hosts**", "**occasionally hosts**" and "**accidental hosts**". These different hosts are selected by the fleas according to availability but were left immediately, if better hosts are close by.

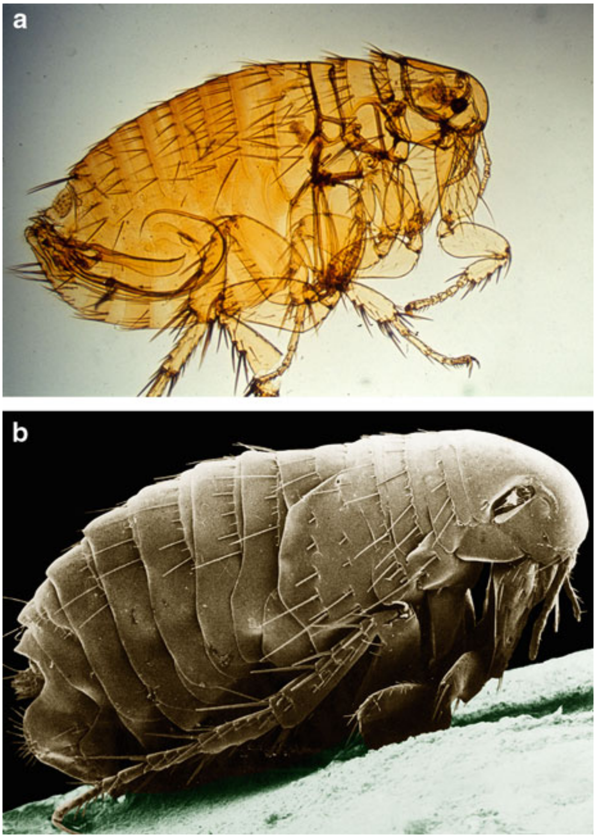
Worldwide about 1600–2000 flea species are described, of which about 80 are found in Central Europe; however, only 5–10 species are important with respect to a potential vectorship of agents of human diseases (Table 5.3). Species diagnosis is difficult and cannot be done just by consideration of the host, where the flea was found.

All flea species have a **holometabolic development**, i.e. they produce larvae. The last larva is transformed into the pupal stage and inside the pupa the adult female or male flea is developed (Figs. 5.34, 5.35, 5.36, 5.37 and 5.38). The whitish eggs are excreted in different series. The females of *Pulex irritans* produce in total up to 450 eggs, while the cat flea (*Ctenocephalides felis*) is able to lay up to 1000 eggs, which are excreted in daily packages of about 25. Thus, a single, fertilized female flea may start a real flea invasion in a dwelling.

The larval development takes about 14 days (at 18–29 °C and at 70–90 % humidity) in the case of the so-called human sandflea *Tunga penetrans*. In the case of chicken fleas (*Ceratophyllus gallinae*), dog fleas (*Ctenocephalides canis*) and cat fleas (*C. felis*), this development is somewhat shorter. The larval development occurs mainly inside/on the resting sites of their hosts. Thus, in order to verify the existence of fleas in a dwelling it is needed to start the search for the whitish, worm-like maggots. The so-called human flea *Pulex irritans*

Figs. 5.37 (**a**, **b**) Scanning electron micrograph of the anterior end of a cat flea (*Ctenocephalides felis*) showing the two typical combs at the ventral and dorsal side of the head respectively at the pronotum (*right side*). (**c**) Diagrammatic representation of the internal aspect of a flea showing that the stiff anterior portion of the stomach is not extendible





Figs. 5.38 External aspects of *Pulex irritans* by light (**a**) and scanning electron microcopy (**b**)

proceeds its development in dusts close to human beds and can only hardly be seen by naked eye. These flea larvae do not suck blood since their chewing mouthparts are unable to penetrate the skin of humans or animals. On the other hand, adult fleas of both sexes have biting-sucking mouthparts (Fig. 5.37). By their help they suck blood several times per day. Thereby they ingest in a hasty manner larger amounts of blood than they can use. Thus, they excrete within their feces dry portions of blood, which then serve as food for their larvae. The last of three larval stages excretes a fluid, which hardens and thus forms the pupal cover. Therein the female or male adult flea is formed within 7–10 days. The whole development from egg to an adult flea is temperature dependent, e.g. in moderate European temperatures it takes about 4–6 weeks. Human fleas and related species need a minimum of humidity, so that in general dry human dwellings are poor biotopes for their progeny. The cat flea *Ctenocephalides felis* (Table 5.3), however, is not very temperature and humidity dependent and thus is now much more common in human dwellings than *Pulex irritans*. This cat flea, which attacks besides cats also dogs and humans, represents now 80 % of the fleas occurring in human dwellings. Inside the pupal cover (cocoon), the ready-to-hatch adult flea may starve for long (up to 1 year) since it waits for soil shakings, which announce the arrival of a potential host. This is important to know for people who move into an apartment, which was the home of dog or cat owners and was empty for a longer time. The newcomers may become attacked by large numbers of suddenly hatching fleas. The same behaviour is described from bird fleas, which rest inside their pupa cover until another bird enters the nest or they attack when humans start cleaning bird cages, etc. Fleas leave dead bodies as soon as the body cools down. This is important in the transmission of the agent of plague—the bacterium *Yersinia pestis*. If infected rats die, the fleas leave them and attack humans, where they transmit the plague bacteria during blood sucking. This transmission occurs by regurgitation of blood containing the bacteria into a human host. This occurs in the following steps:

(1) A flea ingests the bacteria at an infected rat.
(2) The flea changes the host and attacks after a while a human being.
(3) The flea starts to suck hastily human blood, which is mixed in its prestomach (Fig. 5.38c) with remnants of rat blood containing the bacteria.
(4) Then the non-stretchable anterior portion of the flea's gut becomes overfilled and as a consequence the flea vomits—regurgitates the whole blood mixture containing the bacteria into the wound of the human skin.
(5) Then the bacteria may start propagation inside human blood.

Especially the tropical rat flea (*Xenopsylla cheopis*, Table 5.3) is a very important vector of the agents of plagues, since it is worldwide common on rats in human slums. From time to time, outbreaks of plague occur even today in regions of India, East Africa and the USA.

Table 5.3 Important flea species

Species	Size (mm)	Characteristics	Hosts
Pulex irritans	♂ 2–2.5 ♀ ~4	Neck without comb-like protrusions, ocellar bristle below eye	**Humans**, pet animals
Ctenocephalides canis, C. felis	♂ 2 ♀ 2.5	1 comb each at head and pronotum	Dogs, cats, **humans**
Xenopsylla cheopis	♂ 1.4 ♀ 2.5	Without any combs, ocellar bristle crosses the eye	Rats, mice, **humans**
Ceratophyllus gallinae	♂ 3 ♀ 3.5	1 comb at the pronotum	Chickens, **humans**
Echidnophaga gallinacea	♂ 1.5–2 ♀ 2–2.5	Without combs; female becomes attached at skin of birds and humans	Chickens, dogs, **humans**
Tunga penetrans	♂ 0.5–0.7 ♀ 0.5–1.0	Pronotum without comb, female penetrates skin, male free running	**Humans**, Many animals, especially rats

3. **Bite reactions**: Fleas are easily disturbed during blood sucking. They stop it and start a new approach at a different site. Thus, there can be found real rows of bites along human skin (Figs. 5.39, 5.40). The injected saliva initiates itching, which is repeated, if one is scratching at a bite site. However, reactions on bites may range from none to extremely intense depending on the allergic status of a host—but in any way they are nasty and remain for several days.
4. **Transmission of agents of disease**: The history of mankind is full of examples, where fleas had influenced the fate of single persons but also that of whole nation, since they are vectors of agents of diseases.
    4.1. **Plague**: This disease, which killed millions of humans in times before the invention of antibiotics, is due to infections with the bacterium *Yersinia* (*Pasteurella*) *pestis.* This gram-negative, stab-like bacterium, which was detected 1896 by former co-workers of Robert Koch (=Yersin, Kitasato) during an epidemy in Hong Kong, is transmitted during regurgitation of bacteria containing blood by fleas. These bacteria reach via blood and lymph the lymph nodes which increase their size extremely within 3–5 days after the flea bite and appear in a haemorrhagic red colour. These swollen regions occur in about 90 % of all infections and were called **bubones**. Via blood transportation the agents of disease then may enter the lung, where they reproduce themselves enormously so that during

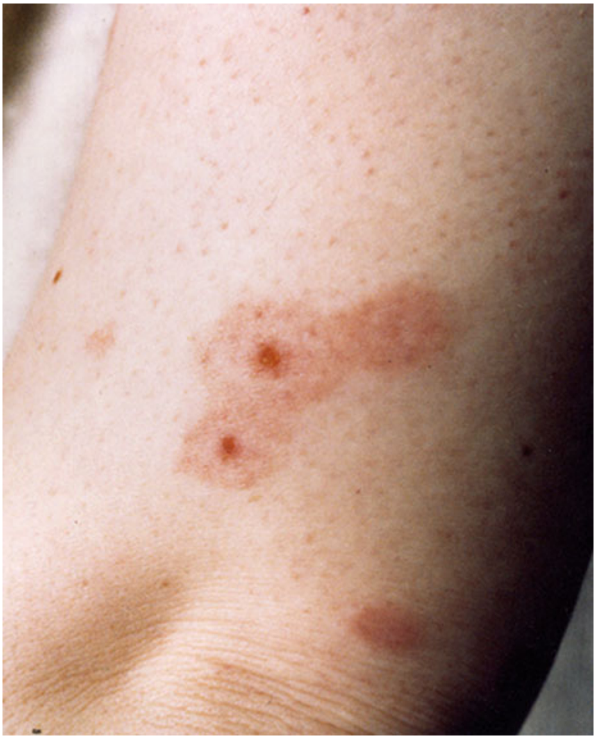


Fig. 5.39 Macrophoto of human skin showing a row of bites of a cat flea

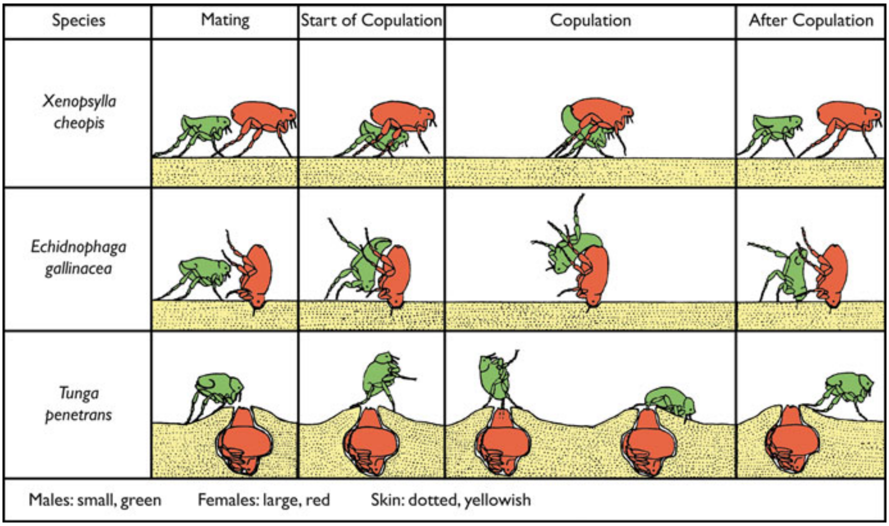


Fig. 5.40 Diagrammatic representation of three different fleas and their behaviour on human skin

coughing slime masses with millions of bacteria are expectorated and may infect other persons. This phase—called lung pest—is lethal without treatment. Thus, it is understandable that in pre-antibiotic time plague has extremely reduced human populations. For example, after the European so-called 30-Year War (1618–1648) as many people were killed that only 5 million humans remained in the region between Breslau and Paris (over a distance of 1200 km). But even today plague is still present in India, Africa and North America. For example, 1994 there was a pest breakout in India close to a monastery (where "holy" rats were kept) leading to thousands of human cases, which made big problems, since the needed supply with antibiotics was too slow. Treatment is done today by application of tetracyclines.

4.2. **Murine spotted fever**: The agents of this and related fevers (*Rickettsia typhi* = *R. mooseri*) are common in rats in many tropical and subtropical regions. Today treatment is done by application of tetracyclines and chloramphenicol. However, extremely important is the intense control of plague hosts such as rats and fleas.

4.3. **Erysipeloid**: This disease is often found in Russia and is induced by the bacterium *Erysipelothrix rhusiopathiae* which leads to severe skin damages in many animals and immune-compromised humans.

4.4. **Viruses**: The groups of Mehlhorn and Mencke (Germany) proved that flea may transmit a broad spectrum of viruses (e.g. Caliciviruses), which are stable enough to survive for a while in the stomach of fleas (Mencke et al 2009). These agents were found as well as in flea saliva as in flea feces, where they remained infectious for up to 60 days.

5. **Flea elimination**: In order to avoid transmission of agents of disease by flea bites or flea feces, the pet animals should be protected by insecticidal collars and pour-on preparations containing insecticides (e.g. Advantix®). The latter, however, do not act against flea larvae, which, however, may be killed by MiteStop®, an extract of neem seeds, which dries up the surface layer and thus kills the larvae.

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5.5.1.1 Human Flea (*Pulex irritans*)

1. **Name**: Latin: *pulex* = flea; *irritans* = annoying. English: Human flea; German: Floh; French: puce.
2. **Geographic distribution/epidemiology**: Today this flea occurs worldwide; however, in early times it was restricted to North America. It is apparently absent in tropical regions of Asia. Humans and their dogs helped to distribute this flea worldwide starting about around 1700. For **size and morphology,** see Table 5.3 and Fig. 5.35).
3. **Transmission of agents of disease**: *Pulex irritans* transmits the agents of plague and erysipeloid and is intermediate host of the tapeworm *Dipylidium caninum*.

5.5.1.2 Cat Flea (*Ctenocephalides felis*)

1. **Name**: Greek: *ctenos* = comb; *cephalon* = head. Latin: *felis* = cat.
2. **Geographic distribution/epidemiology**: Today worldwide.
3. **Biology, morphology**: This flea (Figs. 5.36 and 5.37) has developed several races, which occur worldwide. Main hosts are still today cats; however, it is also very common on dogs and humans, where it represents 80 % of the infestations. It is also common on rats, mice and several other free-living mammalians. Even birds were found bearing this flea. It has its origin in regions of North Africa and Asia and was imported to Europe especially in times of the Roman Empire. Its spread increased in Central Europe, when cats became "house animals" in the thirteenth–fourteenth century. Its reproduction is considerably increased in human dwellings. This is understandable, since it originates from "warm" countries. The recent occurrence relation of cat fleas to the human fleas is 18:1, underlining its dominance in human dwellings.
4. **Transmission of agents of disease**: Worldwide: vector of agents of plague and potential mechanical transmission of several viruses. Furthermore, this flea may become intermediate host of the tapeworm *Dipylidum caninum*.

5.5.1.3 Dog Flea (*Ctenocephalides canis*)

1. **Name**: Greek: *ctenos* = comb; *cephalon* = head. Latin: *canis* = dog.
2. **Geographic distribution/epidemiology**: Worldwide.
3. **Biology, morphology**: Both sexes of this flea (see Table 5.4) suck blood at a very large spectrum of animals and humans. In southern European countries, about 50 % of the fleas on humans are dog fleas. It needs microscopical investigation to differentiate dog fleas from cat fleas (Table 5.4). Dog fleas can be differentiated from cat fleas by the help of the length of the first tooth at the lower side of the head. The first tooth is half as long as the second one, while in cat fleas the first and second teeth are identically long.
4. **Transmission of agents of disease**: Worldwide: plague; In Europe and East USA: the tapeworm *Dipylidium caninum*.

Table 5.4 Some common parasitic bugs

Family/Species	Length (mm)	Hosts
Reduviidae		
Rhodnius prolixus	30	**Humans**, many animals
Triatoma infestans	30	**Humans**, many animals
Panstrongylus megistus	30	**Humans**, many animals
Reduvius personatus	18	Insects, **humans**
Cimicidae		
Cimex lectularius	5–6	**Humans**, mammals, birds
Cimex hemipterus	6–7	**Humans**, mammals, birds
Oeciacus hirundinis	2–3	Swallows, **humans**
Leptocimex boueti	3–4	Bats, **humans**

5.5.1.4 Bird Fleas

The flea species of birds are very common. However, humans are mostly infected only in cases of contacts to birds, e.g. when cleaning nest boxes. Then numerous fleas may attack humans at the same time, since up to several hundred (or even thousands) may be present inside nest boxes. The most common species are the chicken flea *Ceratophyllus gallinae*, the flea of doves *Ceratophyllus columbae* and the peculiar flea *Echidnophaga gallinacean* (Fig. 5.40). Bird fleas are vectors of a broad spectrum of agents of diseases of chicken (Table 5.4).

5.5.1.5 Rat Fleas (*Nosopsyllus fasciatus*)

1. **Name**: Greek: *nosos* = disease; *psyllos* = flea. Latin: *fasciatus* = striped. English: Northern rat flea.
2. **Geographic distribution/epidemiology**: This flea is worldwide distributed and acts as a mechanical vector of several agents of disease.
3. **Biology, morphology**: Main host is the so-called migrating rat (*Rattus norvegicus*). In addition, other hosts may be used: e.g. rodents and carnivores, which feed such rodents. Occasionally also humans are infested. Thus, it is not astonishing that it occurs like the mouse flea *Leptopsylla* (*Ctenopsyllus*) *segnis* also on cats. This fleas also enter easily humans. The tropical cat flea *Ctenophyllus cheopis* is the main vector of agents of plague.
4. **Transmission of agents of disease**: Plague bacteria in the USA; worldwide: agents of pseudotuberculosis and erysipeloid.

5.5.1.6 Sandflea (*Tunga* (*Sarcopsylla*) *penetrans*)

1. **Name**: Latin: *intingere* = immersing; *penetrare* = penetrating. Greek: *sarx* = meat, flesh; *psylla* = flea. English: Jigger, sand flea, chigoe flea.
2. **Geographic distribution/epidemiology**: This flea is found in Central and South America, in tropical Africa as well as now in Australia, where it was apparently imported.
3. **Biology, morphology**: *Tunga penetrans* and several related species attack humans and a broad spectrum of animals. These fleas are rather tiny (Table 5.4; Figs. 5.41, 5.42, 5.43 and 5.44). The males stay on the bodies of their hosts and

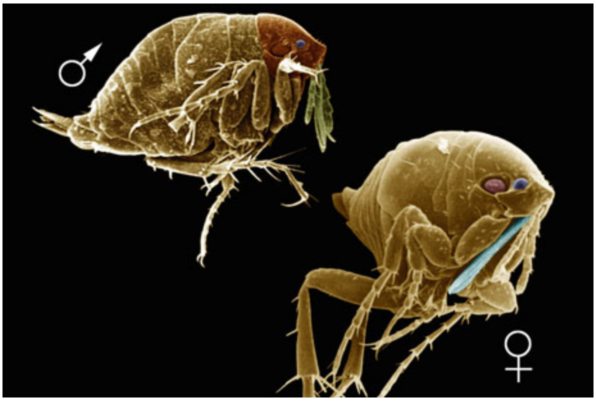

Fig. 5.41 Scanning electron micrograph of a male and female *Tunga penetrans* flea. Note the protruded copulatory apparatus of the male

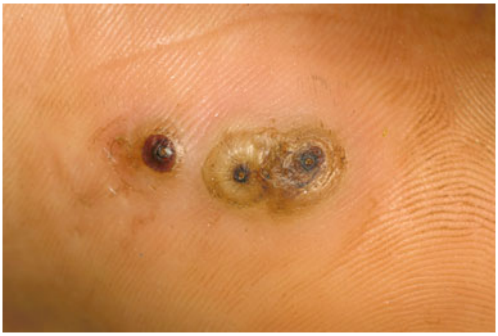

Fig. 5.42 Macrophoto of human skin infested with three females of *Tunga penetrans*. Only the terminal poles are seen. The diameter of each of the swollen females is 7–8 mm

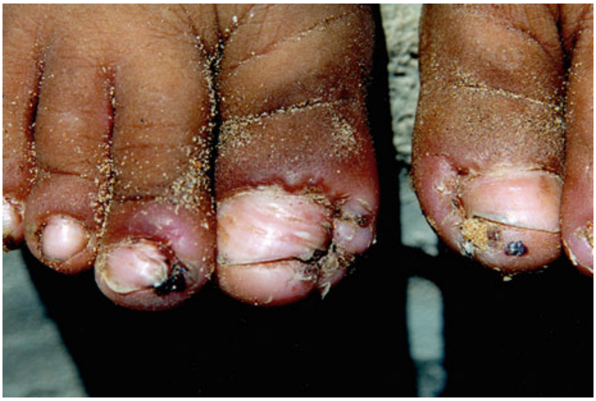

Fig. 5.43 Toes of children with penetrated females of *Tunga penetrans* fleas

"visit" there the females which have entered (head forward) the skin of their host. Only the abdominal end can be seen (Figs. 5.42 and 5.43). The males fertilize the females, which produce several thousands of eggs that drop down to the soil. The larvae hatch on the soil (often in sand) and moult only once, since they have in contrast to other fleas only two larval stages. The larva 2 excretes the pupal sheath inside which the adult stage is developed. The time needed for the total development from the egg to the adult stage is mostly not longer than 3 weeks. Female fleas mainly attach at the feet of larger hosts such as dogs, rats, pigs, cattle and humans, while the smaller males never enter the skin of hosts. At the entrance site the females mostly choose the soft skin regions of the feet. Thus, they are often found between the toes and below the toenails (Figs. 5.42, 5.43). However, also other regions of the human skin may become penetrated (e.g. hands, elbow, genital region). The females enter the selected places head forward. However, they never enter completely. The terminal end of the abdomen remains always visible, since there are the openings of the sexual organs and those of their tracheal system, which is needed in order to obtain sufficient oxygen (Fig. 5.42). After its penetration into the skin, the female abdomen increases within 8–10 days its size up to that of a pea (Fig. 5.44), since the

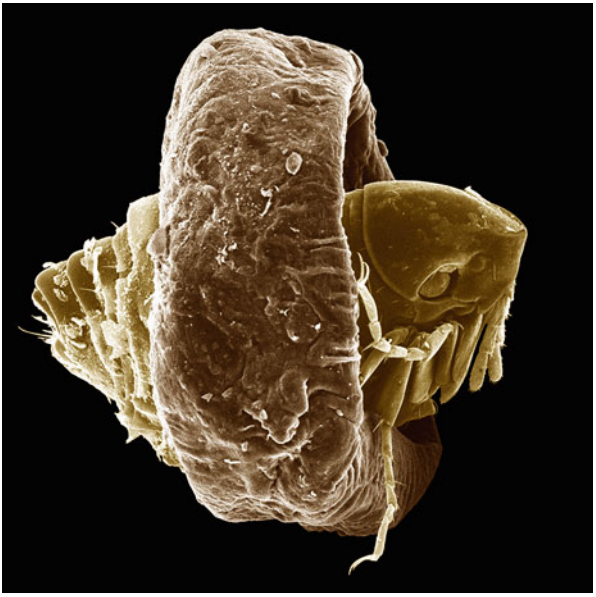

Fig. 5.44 Scanning electron micrograph of a female of *Tunga penetrans* extracted from human skin. Note that especially the anterior portion of the abdomen is swollen, since therein the ovarian tubes have produced numerous eggs

ovaries produce several thousands of eggs, which are discharged at their terminal pole, from where they drop to the soil. The males had fertilized them by injection of masses of sperms when introducing their protrudable, penis-like sexual organ (Fig. 5.41) into the sexual opening of the female.

4. **Treatment**: The females have to be removed carefully by surgical methods from the skin in order to avoid secondary infections after they had been killed in the skin by application of fine oils. After this the wounds have to be covered with antibiotic compounds in order to avoid blood poisoning.
5. **Prophylaxis**: Wearing closed shoes in endemic regions is the best protection against attacking sand fleas. In addition the application of icaridin-containing repellents such as Viticks® or Autan® keeps away lurking fleas.

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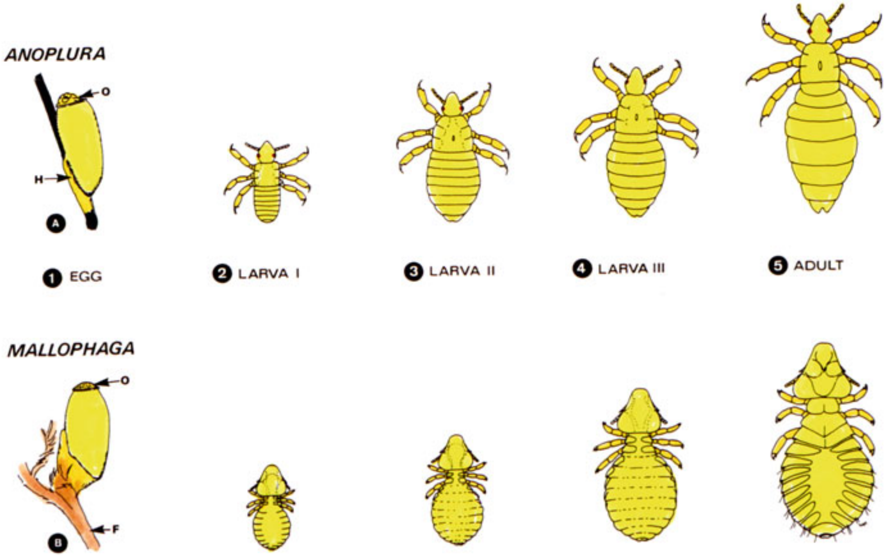

Fig. 5.45 Diagrammatic representation of the life cycle of the bloodsucking lice (Anoplura) and of the chewing lice (Mallophaga). *F* feather; *H* hair; *O* operculum

5.5.2 Lice (Phthiraptera)

1. **Name**: Old German: *Luizen* = lice. Greek: *phtheir* = louse; *anoplos* = without sting; *ura* = tail; *phagein* = feeding. Latin: *apterus* = without wings; *malleus* = hammer; French: pous; German: Laus.
2. **Biology, morphology**: In principle two types of lice exist (Fig. 5.45):
   - **Anoplura** (bloodsucking lice),
   - **Mallophaga** (biting lice).

In the case of the Anoplura, the head is smaller than the thorax, while in the Mallophaga the head is clearly broader than the thorax (Fig. 5.45). Anoplura have retractable sucking mouthparts, while Mallophaga possess biting ones, which are not retractable. The specimens of both groups have strong claws at their legs, by the help of which they may become attached at the hair of their vertebrate hosts.

The medicinal (for humans) important bloodsucking lice (Anoplura) are rather host specific. The genus ***Pediculus*** comprises two species. One of which (*P. schaeffi*) parasitizes on chimpanzee monkeys, while the other includes two subspecies (*P. humanus capitis, P. humanus corporis*) and is found exclusively on humans. While *P. humanus capitis* is at least 5 million years old, *P. humanus corporis* has become an individual species when humans started to wear different clothes (i.e. before about 40,000 years). The genus ***Phthirus*** comprises two species: one on gorillas (*P. gorilla*e) and one (*P. pubis*) on humans, which is worldwide distributed.

All bloodsucking lice have several common morphological features:

- The head is provided with one pair of antennae, which each contain five segments bearing smelling sensilla (Figs. 5.46, 5.47, 5.48 and 5.57).
- The two eyes consist each of a single, but enlarged, pigmented ommatidium (Fig. 5.49, 5.50).
- The three pairs of legs consist of five segments (coxa, trochanter, femur, tibia and tarsus (Fig. 5.45).

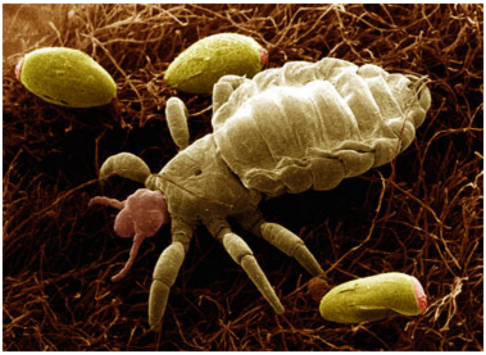

Fig. 5.46 Scanning electron micrograph of a female body louse (*Pediculus humanus corporis*) and some eggs glueing at tissue

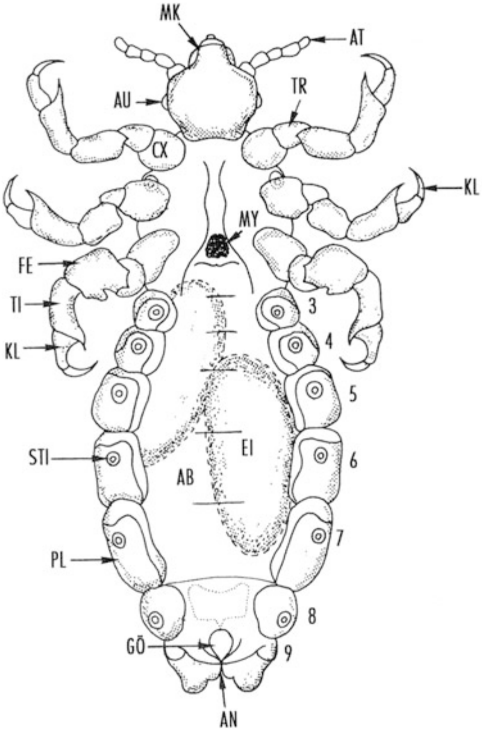

Fig. 5.47 Diagrammatic representation of a female head louse from its dorsal side. *A* abdomen; *AN* anus; *AT* antenna; *AU* eye; *CO* coxa; *EI* egg; *FE* femur; *GÖ* genital opening; *KL* claw; *MK* snout; *MY* mycetome (bacteria); *PL* lateral plate; *STI* stigma; *TR* trochanter

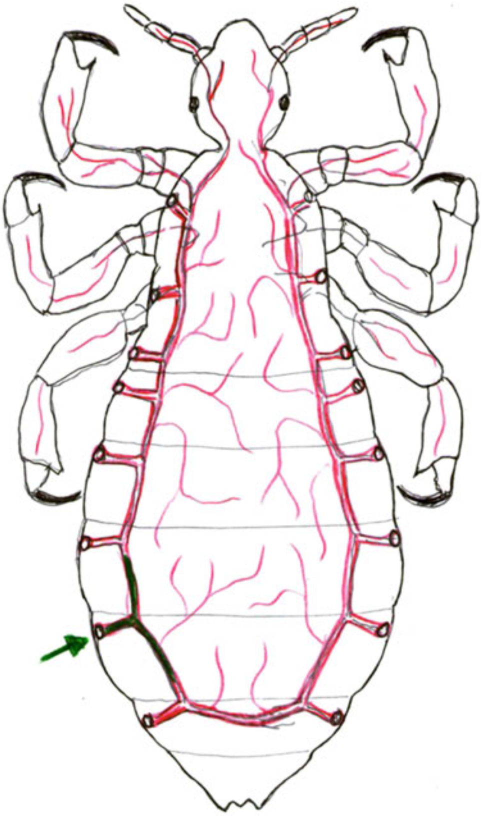

Fig. 5.48 Coloured drawing of the tracheal system of head lice. Only the very large lateral channels are drawn. The air enters into this tracheal system via the stigma, which are connected with the internal system (*green arrow*)

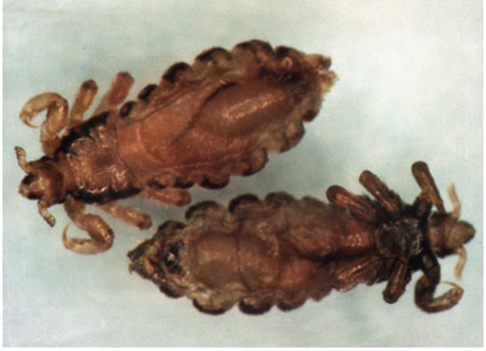

Fig. 5.49 Light micrograph of two females of *P. h. capitis*, each showing the protrusion of an egg in the hindbody

- The two claws of each tarsus may clutch ring-like together, so that a hair can be completely surrounded. Thus, an accidental dropping down from a host is avoided (Fig. 5.51).
- The mouthparts belong to the biting-sucking type and are kept retracted in a sheath inside the head until next blood sucking (Fig. 5.50);

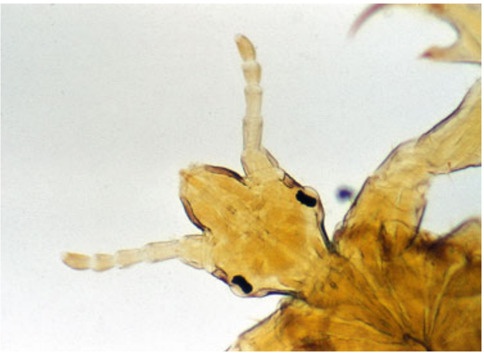

Fig. 5.50 Light micrograph of the head of a female louse showing the two lens eyes with pigment, two antennae (each with 5 segments) and the two sucking channels retracted into the snout

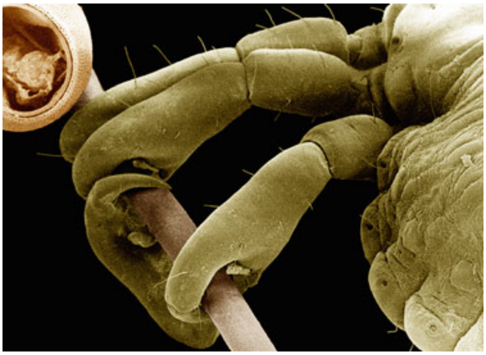

Fig. 5.51 Scanning electron micrograph of the lateral aspect of a head louse being attached by the help of its claws at a hair close to an empty egg. Note that each segment (*right*) is provided with a single stigma

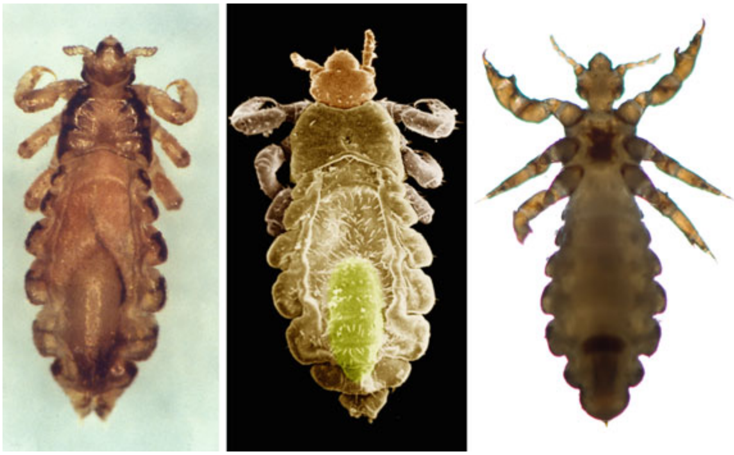

Fig. 5.52 Light micrograph of a male stage showing the protruding "penis" at the terminal end

- Lice are wingless in all stages (3 larvae, ♀ ♂ adults and thus have to be transmitted during hair-to-hair contacts of their human hosts (Fig. 5.45)).
- The egg-like appearing abdomen consists originally of ten segments (Fig. 5.47). The first two are strongly reduced and do not bear openings. But starting from the third until the eighth segment each has an opening of the tracheal (=breathing) system (stigma, spiracle) at each lateral side. The terminal segments 9 and 10 are fused.
- The males are somewhat smaller than the females (Fig. 5.51) and possess a pike-like, protrudable penis (Fig. 5.51). The sperms are produced inside two testes (each with two lobes) from where a ductus seminalis transfers the sperms to two sperm bladders that are provided with glands. Finally the ends of these bladders are united and terminate in an injector (penis), which may be injected into the female system.
- The **sexual opening** of the females is situated at the terminal end of the abdomen and can be recognized by a bifurcated structure, into which the penis is injected (Fig. 5.47).
- The **female sexual system** consists of two ovaries each with five tubes containing the produced eggs. After fertilization the eggs are excreted via the two oviducts, which are lined by symbiotic microorganisms and are transferred to the eggs. The oviducts fuse, thus producing a single terminal portion which does not form a typical receptaculum seminis, but is lined by two glands (each with three lobes) excreting a glueing material that finally covers the eggs. The females are thus able to attach them firmly at the hair close to the scalp. Due to the lack of a receptaculum seminis, the lice have to copulate several times during their rather short life time as adults (2–3 months).
- The thorax comprises three segments being closely melted; at the dorsal side, there appears a central depression, which is not a spiracle (=opening of the breathing system), but occurs due to the fact that at its inner side strong muscles are affixed. The dorsal side of the lice does not possess or any residuals of them at any stage of the development. The thorax bears on each side one spiracle = stigma = opening of the respiratory system.
- The eggs are glued at the hair and possess an apical operculum with typical aeropyles (openings) through which oxygen may enter (Figs. 5.53, 5.54, 5.55 and 5.56).

5.5.2.1 Body Louse (*Pediculus humanus corporis*)

1. **Name**: Latin: *pes, pedis* = foot; *pediculus* = small foot; *humanus* = human; *corpus* = body.
2. **Geographic distribution/epidemiology**: This subspecies is worldwide distributed.
3. **Biology, morphology**: The larvae and adults suck blood along the body of humans and the female glues its eggs at human body hair, but also at clothes

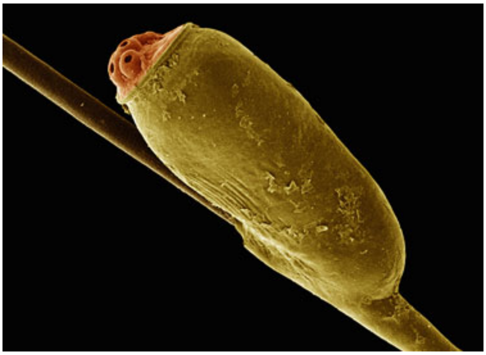

Fig. 5.53 Scanning electron micrograph of an egg of *P*. *humanus capitis* showing the operculum (cover) which is provided with aeropyles

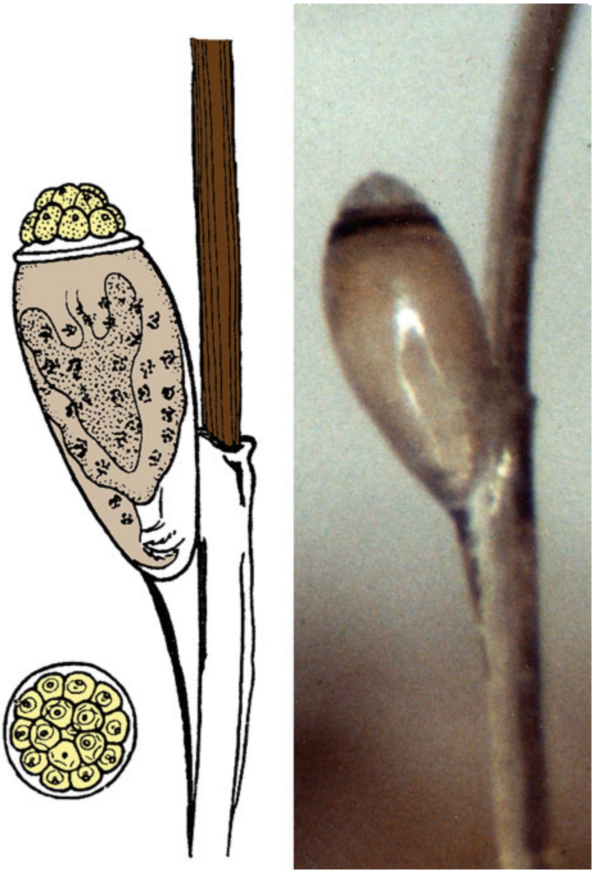

Fig. 5.54 Diagrammatic representation (*left*) and light micrograph of an egg (nit) of *P*. *humanus capitis* attached to a human hair

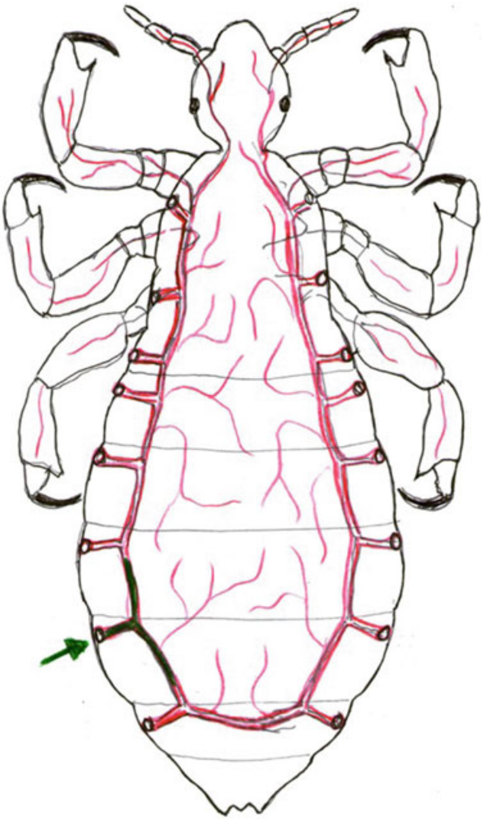

Fig. 5.55 Diagrammatic representation of the breathing system (tracheal system) of lice (with openings (*arrow*) at the lateral side of the segments)

and bed covers (Figs. 5.46, 5.47 and 5.48). Their temperature optimum ranges between 31 and 33 °C. They leave persons with very high fevers. Thus, they are found more often in moderate climates than in the tropics. They occur there mainly in rain periods. Temperatures higher than 50 °C kill these lice and their eggs within about 30 min. At 90–100 °C they die within one minute. Starving is tolerated only for short at higher temperatures, but they survive deep temperatures for a while or incubation in cold water. However, body lice need at least one blood meal per day at body temperatures, but may survive colder phases (e.g. when clothes are stored away from the human body). Female adults live for 30–40 days and produce during this time up to 300 eggs = about 5–15 eggs per day. The larvae hatch after about 7 days and it takes another 8–15 days and three moults until the adults are developed, so that a body louse population is spreading very quickly inside a dwelling. 20,000 lice have been found as maximum infestation of a single person.

4. **Diagnosis**: The diagnosis of an infestation with body lice can be done easily by examination of clothes for attached lice and eggs as well as for feces which appear as dense glueing particles.

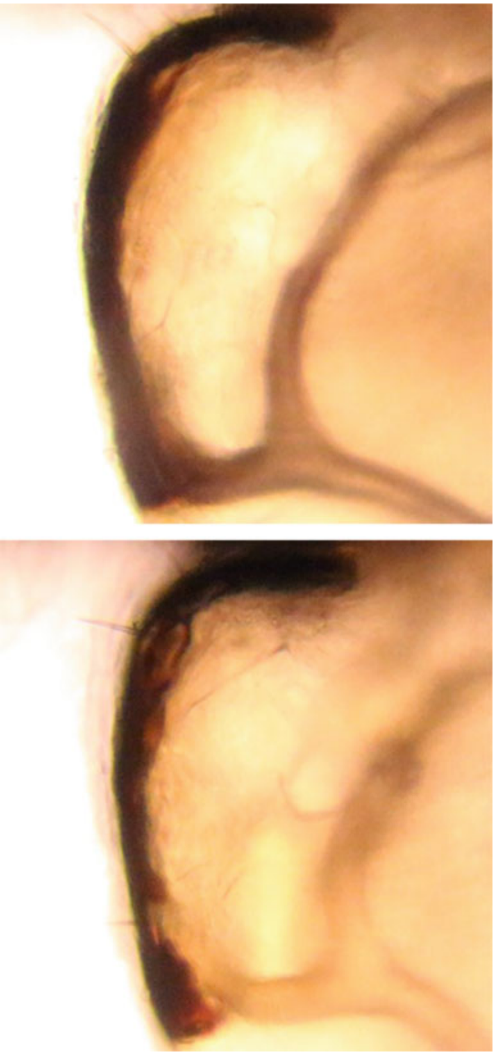

Fig. 5.56 Light micrographs showing the spiracle before (=empty) and after (=full) the entrance of the anti-louse shampoo Licener®

5. **Symptoms of bites**: The biting sites appear first as a red, 1 mm sized dot, which later appears bluish. The feeling of itching varies among infected people from light to strong and to very intense depending on the grade of individual sensibility. Due to scratching, bacteria may superinfect the biting sites so that eczemas or larger ulcera may occur. In cases of a high density of lice on a body, the skin may appear brownish.
6. **Transmission of agents of diseases**: In contrast to head lice, body lice may transmit several agents of disease:
   (1) **Louse borne spotted fever**: This disease which is also called **spotted typhus** occurs due to an infection with *Rickettsia prowazeki* [being named

honouring the American scientist Howard Tyler Ricketts (1871–1910) and the collaborator of the Nobel Prize winner (1905) Robert Koch: Stanislaus von Prowazek (1875–1915)]. These agents occur in Europe, Africa and Asia. The **transmission** takes place by inhaling the rickettsial stages within the dry, dust-like feces of infected body lice. However, transmission may also occur when louse feces are rubbed into itching biting sites. Inside the body of humans, the *Rickettsia* stages enter endothelial cells of blood vessels and destroy them during heavy propagation. After disruption of such cells the *Rickettsia* stages are set free and enter other cells. **Clinical picture**: After an incubation period of about 10–14 days a high, long-lasting fever (at least for 10 days) occurs, which is accompanied by the appearance of skin spots with diameters of about 2–4 cm, dizziness, coughing and severe pain along legs and arms. In untreated cases, 10–20 % of the infected persons die. **Treatment** is done today by the use of **doxycycline** or **tetracyclines. Diagnosis** is done by stained blood smears. The *Rickettsia prowazeki* stages may persist (even after clinical healing) inside RES cells and induce a new outbreak (**Brill–Zinsser's disease**) within the next 20 years. The **diagnosis** can then be done by the use of the so-called **Weil–Felix reaction**.

(2) **Five days fever (Wolhynic fever, trends fever)**: This disease occurs due to an infection with *Bartonella* (syn. *Rickettsia*) *quintana*. After an incubation period of 5–20 days, fever occurs all 5 days. In general, 3–12 of such fever phases may follow each other—often being followed by recidives. The *Rickettsia* stages are found permanently in the peripheral blood so that bloodsucking body lice may permanently become infected in groups (e.g. soldiers) living close together. These rickettsial stages do not enter the intestinal cells of the lice, but glue at their surface, and thus is reproduced extracellularly. This disease is much less dangerous than the spotted fever and death cases are rare. However, infected persons may be contagious for up to 1 year. **Therapy** is done by the use of **doxycycline**.

(3) **European (endemic) relapsing fever**: This fever, which is also called louse-relapsing fever and based on infections with spirochaetes (*Borrelia recurrentis*), is transmitted by body and head lice. However, it is transmitted neither by biting nor by ingestion of flea feces, but only when people squeeze lice and thus get oral contact with these bacteria. This agent of disease is still today of importance in North Africa and America.

Clinical aspects: After an incubation period of about 8 days, sudden shivering occurs followed by fevers up to 41 °C followed by strong weakness and headache. This fever period keeps on for up to 5 days. After several days without shivering, a relapse fever occurs followed again by a fever-free phase and so on. The symptoms decrease with each phase. However, the clinical picture shows enlargements of the spleen and liver accompanied by a mild icterus. Along the skin maculae, papulae and petechial alterations may occur. Occasionally also meningoencephalitic symptoms have been diagnosed. There are also described dysfunctions of the brain nerves and cramps. Lethal cases occur due to myocarditis, cerebral bleedings and/or liver dysfunction.

Diagnosis can be done by microscopical documentation of the *Borrelia* stages in blood smear preparations or by the help of the thick-droplet method, whereby the twisted appearance of the bacteria is most helpful. After a successful diagnosis, treatment can be started by the help of tetracyclines, chloramphenicol or penicillin. In the cases of pregnant women and children below 8 years, amoxicillin or erythromycin should be used.

Further Reading
See Sect. 5.5.2.5.

5.5.2.2 Head Louse (*Pediculus humanus capitis*)

1. **Name**: Latin: *pediculus* = small foot; *caput* = head; *humanus* = human.
2. **Biology, Morphology**: Both sexes of the head louse (♀ = 2.6–4 mm; ♂ = 2.4–2.9 mm) are smaller than those of the body louse; however, the abdomen of the head louse is deeper segmented and the longitudinal muscles of the fourth abdominal segment are completely absent in females (Fig. 5.49). The head lice are mainly found among the hair of the head and rather seldom inside the beard, body hair or eyebrows. Head lice prefer temperatures around 28–29 °C and in the Tropics they may better develop than body lice, although lower temperatures are better tolerated than higher ones (40–50 °C). At temperatures below 12 °C, eggs were no longer produced.

   The head lice glue their ovoid eggs, which measure 0.5–0.8 × 0.2–0.3 mm, by the help of a so-called water-insoluble cuff at the hair (Figs. 5.53, 5.54). The water-insoluble substance is also spread over the whole surface of the egg (nit), which thus becomes protected from drying. The nit is covered at its anterior end by a removable operculum, which shows openings (**aeropyles**) at the tip of protrusion (Figs. 5.53, 5.54). These openings allow the entrance of oxygen into the nit, where the growing embryo is covered by a fine separate layer, which protects from drying. Females lay per day 2–8 eggs during its 3–4 weeks long adult life, so that in general a total of 90–200 new lice are produced. The development inside the egg takes 7–11 days, while the further development via three larval stages (Fig. 5.45) needs another 10–12 days. However, the speed of the development depends on the outer temperature. In any way the transition of a single, fertilized adult female louse from one host to another may induce there a quickly growing and finally large population. In general only fertilized females creep up to the surface of the hair, while male and larvae stay mostly close to the surface of the head skin, since they need often repeated blood meals (every 2–3 h). The fertilized females stay also not very long at the surface of the head hair, but creep quickly back to the surface in order to ingest again blood and to depone there further eggs. In case they get contact with the hair of another person they switch to this person and become thus the mother and grandmother of the population of the new host. The male lice (Fig. 5.52) measure 2.3–2.9 mm in length, while the females are somewhat longer (2.6–4.0 mm) (Fig. 5.49).

3. **Bite reactions**: The injection of saliva during blood sucking leads to itching. Scratching may introduce bacteria into the fresh wounds, which then become inflamed and may develop eczemas.
4. **Epidemiology**: During the last 10 years infestation with head lice increased constantly worldwide due to several reasons (e.g. increased tourism, spreading of refugees, living close together, increasing loss of activity of anti-louse compounds, etc.). Thus, billions of Dollars, Euros, etc., are spent per year in many countries of the world, which would be needed urgently for other purposes. Thus, many governments have released strict laws to reduce louse infestations in public institutions. For example, in Germany children become excluded from visiting kindergarten and school until they prove to be louse free by documentation of a relevant treatment.
5. **Therapy/prevention**: Therapy of lice infestation poses problems since worldwide many anti-louse compounds do not work anymore or have reduced activity. This is the recent situation:
   - **Organophosphates** are in most countries forbidden due to severe health endangering.
   - **Insecticides** (such as permethrin, allethrin, etc.) have lost much of their efficacy in many countries due to the development and wide spreading of resistances of the lice;
   - **Plant extracts** such as oils compounds of *Eucalyptus* trees, etc., may induce severe allergies and reach mostly only a very low efficacy and are often highly inflammable.
   - **Silicones and dimethicones** are active, but glueing, have mostly to become removed by separate intense washing and are often highly inflammable; during the often needed long phases of use some of the products may also influence badly the lung systems.
   - **Shampoo-containing and de-oiled extracts of Neem seeds (Licener®)** act by suffocation and kills the lice within 3–10 min, is not inflammable and is easy to wash out (Figs. 5.55 and 5.56).

Further Reading
See Sect. 5.5.2.5.

5.5.2.3 Pubic Louse (*Phthirus pubis*)

1. **Name**: Greek: *phtheir* = louse; *pubis* = pubic. French: *papillon d'amour* = butterfly of love; German: Filzlaus.
2. **Biology, morphology**: *P. pubis* occurs worldwide and is mainly found in the pubic hair, but enters also eyebrows (Fig. 5.59) and hair of armpits as well as occasionally head hair. The body shape of these pubic lice is so characteristic that it cannot be mistaken for other louse species (Figs. 5.57, 5.58). The adults of both sexes are rather small measuring only 1.6–1.8 × 1.3–1.5 mm. The females

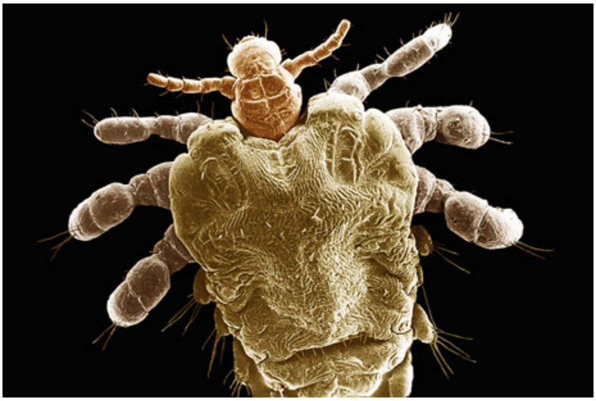

Fig. 5.57 Scanning electron micrograph of an adult female of *Phthirus pubis*. Note the compressed body, where no separation between thorax (breast) and abdomen (hindbody) can be seen

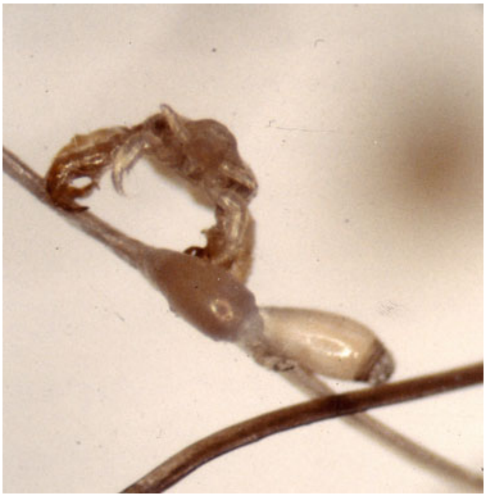

Fig. 5.58 Macrophoto of an adult female *Phthirus pubis* louse and two of its operculated egg glueing at a hair

have as adults a lifespan of about 26 days; the larvae hatch already after 5–8 days from their typically operculated eggs (Fig. 5.59). The three larval stages need another 15–17 days to reach maturity. These lice do not move much and take their blood meal mainly at the same place. Host infections mainly occur during sexual intercourse. Children are therefore not or only low-grade infected.

3. **Bite reactions**: The saliva injected during blood sucking introduces mostly only a low-level itching. Scratching at biting sites, however, may lead to inflammation and formation of eczemas. Skin sites with many pubic lice may appear bluish and thus the French population described these spots as “tâches bleues” = blue spots.
4. **Treatment**: The treatment of an infestation with this “papillon d’amour” is no longer done with the famous mercury containing “grey ointment” during the early years of the nineteenth century in France, but with safe special shampoos such as Licener® (Figs. 5.55, 5.56).

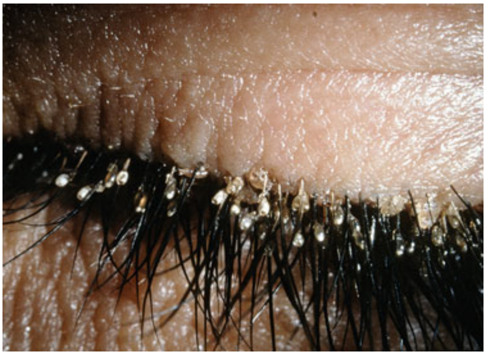

Fig. 5.59 Macrophoto of several eggs (nits) of *P. pubis* glueing at the eyebrow of a female person

Further Reading
See Sect. 5.5.2.5.

5.5.2.4 Further Lice Species

Many lice of animals (e.g. *Haematopinus suis* of pigs, *Linognathus setosus* of dogs) may also infest humans. However, the specimens of these species stay not very long on humans. Apparently they are not adapted to feed on human blood. Furthermore also so-called biting lice (Mallophaga, Fig. 5.44) are able to infest humans (e.g. farmers) for a short while. Due to feeding at the epidermis, there may occur some damages and noticeable itching. However, infestations are finished mostly after short time.

5.5.2.5 Further Reading (Lice)

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5.5.3 Bugs

5.5.3.1 Bedbugs (*Cimex lectularius*)

1. **Name**: Latin: *cimex* = bug; *lectularius* = belonging to the bed; French: punaise; German: Bettwanze.
2. **Biology, Morphology**: The 5–6 mm long bedbugs occur worldwide. They ingest blood during night not only at the body of humans but accept also a broad spectrum of animals (domestic and wild ones). Their former hosts had probably been birds, but now they are also adapted to mammalians.

   The body of bedbugs is dorso-ventrally flattened and thus these bugs are also called "bed flounder" (Figs. 5.60, 5.61 and 5.62). The head shows two compound eyes and two antennae with four segments (Figs. 5.61 and 5.62). For their bloodsucking activity they have developed a protrudable trunk, which contains two tubes formed by the mandibles and maxillae. Via one tube saliva is injected into the wound, while the other sucks the fluid blood. At the dorsal side of the

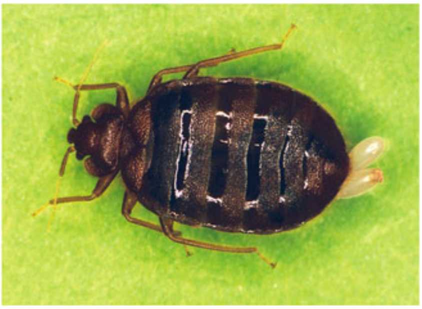

Fig. 5.60 Light micrograph of a female bedbug (*Cimex lectularius*) excreting eggs

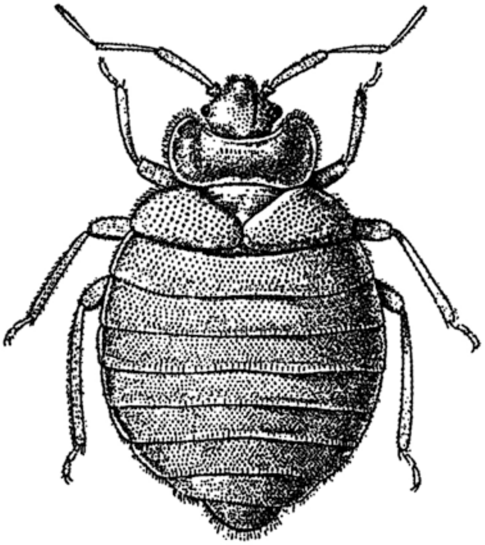

Fig. 5.61 Diagrammatic representation of a bedbug. Note the fine bristles along the surface

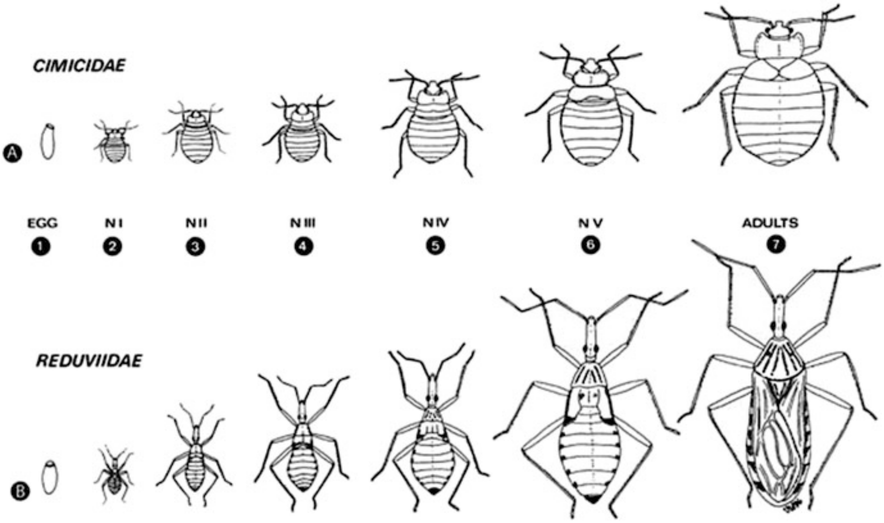

Fig. 5.62 Life cycle stages of the w ingless Cimicidae (**a**, *Cimex lectularius*, bedbug) and the Reduviidae (**b**, *Rhodnius prolixus*) in dorsal view. (**1**) The eggs are laid in batches by *Cimex* and mostly singly by *Rhodnius* in the crevices of bed frames, walls, or similar household sites. (**2**) The larvae (nymphs I) which hatch from the eggs are wingless and feed (as do all other stages) by sucking the blood of humans and also many other mammals. (**3–7**) Five moults of the nymphal instars are needed to reach the sexually mature female or male stage (**7**); in Reduviidae typical fore- and hindwings are eventually formed, but Cimicidae remain wingless in all stages

mesothorax (middle segment between prothorax and metathorax of the breast), remnants of two wings can be seen. The males appear somewhat more slender than the females, which possess a small stiletto-like protrusion being used during copulation. Characteristic are so-called "stinking glands", which have their openings at the "hips" = coxae of the two "hindlegs". Their excretions are used as recognizing tool among bedbug population inside a dwelling—but humans realize this smell as unpleasant stench.

The females depone 1–12 eggs by the help of a glueing substance as well as their feces at hiding places (in beds, behind wall papers, etc.), where they spend the daytime. During night they suck blood—(larvae as well as both sexes of the adults). The development of the bedbugs is hemimetabolous, i.e. they have no pupa stage, but all five larval stages (nymphs) look already like the adults. Between each moult at least one blood meal is needed. The whole developmental cycle takes about 6–8 weeks at room temperatures of 22–24 °C. In cultures adult bedbug lived up to 1 year under constant feeding. If there are no hosts, bedbugs may starve at low temperatures for up to 6 months, if there is not too much heat, while low temperatures are well tolerated. The bedbug *C. lectularius* is not an effective vector for defined agents of diseases, although "mechanical transmission" by contaminated mouthparts had been described or apparently occurred by uptake of fecally contaminated food.

3. **Bite reactions**: The bites are painless; however, nevertheless the skin may react by formation of a more or less strong itching elevation. Since bedbugs suck blood at different places, even a small number of bugs may introduce a large number of itching sites (Fig. 5.63). Although strong allergic reactions may occur in some persons, others may have none and in again others the reactions on bedbug bites are constantly reduced after several series of bites.
4. **Control measurements**: The control of bedbugs inside dwellings poses today no problems. However, since the used insecticides are not harmless, they should spread by a professional desinfector. However, it is absolutely needed to spray the insecticides directly into/onto all hiding sites and to open afterwards the windows of treated rooms for some hours.

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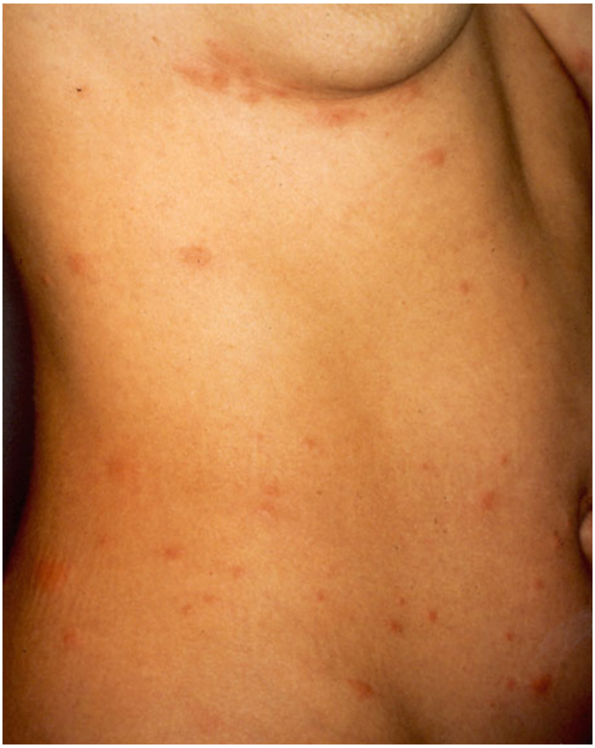

Fig. 5.63 Photo of the body of a patient, who had slept in a hotel room with bedbugs for one night

5.5.3.2 Further Bugs

Tropical Bedbugs

The species *Cimex hemipterus* and *C. rotundatus* (Table 5.5) attack humans in warm and tropical countries. They look like *Cimex lectularius*, but their prothorax is less broad, their head is rather small and long, their abdomen is slender and their whole body is rather dark. Their second abdominal segment is the broadest one, while in the case of *C. lectularius* the third one is the broadest. The species *C. hemipterus* reacts very sensitive on dryness and low temperatures.

Bird Bugs (*Oeciacus hirundinis*)

This species lives in the nets of the house martin in Europe, while *O. vicarious* occurs in swallow nests in America. Both bug species overwinter in the empty nests and starve until the swallows come back. Some individuals may also enter close by rooms of humans and may suck blood there.

Bat Bugs (*Leptocimex boueti*)

This species occurs in West Africa and enters also human dwellings.

Table 5.5 Identification criteria for important mosquito genera, which occur worldwide in huge numbers of species

1a)	Maxillar palps: long; shield: regularly rounded	***Anopheles***
1b)	Maxillar palps: short; shield: three lobes	**2**
2a)	Hindbody is tapered with long cerci or the claws of the anterior feet possess teeth	***Aedes***
2b)	Hindbody rounded; claws without teeth	**3**
3a)	Scales of wings are very broad	***Mansonia*** (*Taeniorhynchus*)
3b)	Scales of wings appear slender narrow or hairlike	**4**
4a)	Large adult mosquitoes (7 mm long, wings 4 mm), spiracular bristles present	***Culiseta*** (*Theobaldia*)
4b)	Midsized mosquitoes (5 mm long, wings 4 mm) spiracular bristles absent	***Culex***

This table represents a selection according to Martini (1952)

Raptor Bugs (Reduviidae)

1. **Name**: The trivial name of these bugs derives from their behaviour to attack during night their hosts and suck considerable amounts of blood; Latin: *reduvivus* = repeated appearance; German: Raubwanze; French: punaise ravisseur.
2. **Biology, Morphology**: Raptor bugs are only of importance in South and Central America, since they are there vectors of the agents of the so-called Chagas disease, which is due to infection with *Trypanosoma cruzi*. For the transmission of *T. cruzi* stages especially the following species are of importance: *Triatoma infestans* (Fig. 5.63), *T. dimidiata, T. maculata, Rhodnius prolixus, Panstrongylus megistus* and the especially large bugs of the genus *Dipetalogaster*. These rather large bugs, which as adults are able to fly (in contrast to bedbugs), possess a nose-like anterior end (rostrum) at the lower side of which the erectable sucking apparatus is anchored (Fig. 5.64). The antennae with four segments and the two compound eyes are seen at the lateral sides. The anterior wings are so-called half wings and serve as cover for the skinny hind wings, which are used for flights. During daytime these raptor bugs live hidden inside houses or close by. Each female may lay up to 2000 eggs. The developmental cycle, within which—depending on the species—up to 7 bloodsucking nymphs may follow each other, takes up to 1 year (Fig. 5.62). The European fecal bug or dust bug (*Reduvius personatus*) (Fig. 5.65) belongs to the group of the above-listed raptor bugs, but it does not act as vector of agents of disease. However, their bites during accidental contacts are rather painful.
3. **Bite reactions**: Specimens of the *Triatoma* species suck blood very often along the skin of the face of sleeping persons (thus they are called “kissing bugs”), but they also suck along legs and arms. The bite itself is not painful and the skin reactions are very different depending on the allergic status of the attacked person.

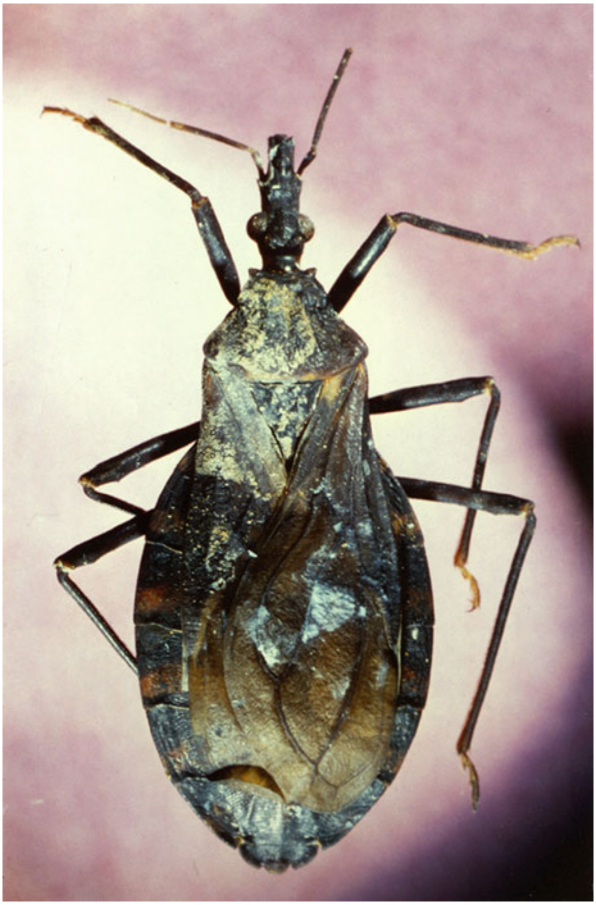

Fig. 5.64 Reduviid (raptor) bug from South America *Triatoma infestans*

4. **Transmission of agents of disease**: The flagellate *Trypanosoma cruzi* is reproduced in the intestine running through a metamorphosis via epimastigotes to the infectious trypomastigote stages, which were excreted within the bug's feces mostly close to the biting site, so that they can be rubbed into the biting channel. Since hungry bugs also suck blood at fully engorged members of their own or related species, propagation of *T. cruzi* occurs also inside of a biotope by transmission within the bug population without involving vertebrate hosts.
5. **Control measurements**: In endemic regions, insecticide spraying campaigns using contact insecticides are organized by governmental authorities. However, true elimination of the parasites (bugs and protozoans) is surely impossible since there exist for both parasites several natural hosts, which cannot become eliminated.

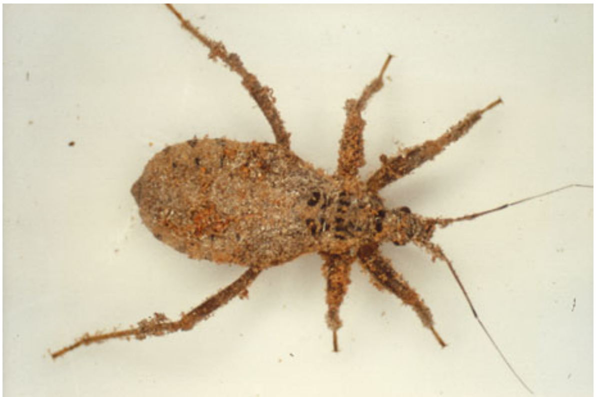

Fig. 5.65 Larva of a so-called fecal bug from Europe, which is covered by dust and thus invisible for prey insects

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Weirauch C et al (2015) *Reduvius frommeri*, a new species of Reduviidae from the Western United States (Hemiptera: Reduviidae), with a synopsis of the Nearctic species of Reduvius Fabricius. Zootaxa 3972:267–279.

5.5.4 Mosquitoes (Nematocera)

1. **Name**: The name has its origin in the Portuguese term *mosquitos* = biting insect. Greek: *nema* = filament; *keras* = horn; French: *moustique*; German: Mücke.
2. **Biology, morphology**: Most of the mosquitoes in nature do suck blood. Also the males of the bloodsucking species do not take up blood. On the other hand, bloodsucking females may be kept in laboratories just on a sugar diet. However, then they do not produce eggs. Since many people do not know that only a few species suck blood (what may be painful), they get in fear, when the large tipulids, dancing winter mosquitoes (=trichoceridae) or the close lakes appearing twitching chironomids are occasionally approaching them.

The species determination of the different mosquito species is difficult due to the large number of existing parasitic and non-parasitic species. Males and females of some important genera can, however, be diagnosed at least at the genus level (Figs. 5.66, 5.67, 5.68, 5.69 and Table 5.5). Males have mostly long lateral hair at their antennae, while females have mostly only few hair-like lateral protrusions along the antennae. The bushy antennae of the males are used to get in contact with females, while the tiny sensory hair at the antennae of bloodsucking females are used to find warm-blooded hosts.

The life cycle stages of three important genera of mosquitoes are presented in Fig. 5.66. The eggs are deponed depending on the genus singly or in groups onto the surface of freshwater (rarely in some species also on saltwater, e.g. *Aedes mariae*). The larvae need oxygen, which they get by the help of siphons brought at the surface of their water biotope (Fig. 5.66). In contrast to many other insects, the pupae of mosquitoes remain motile, but do not feed. They obtain their oxygen also by swimming at the surface of a biotope. Prior to the hatch of the adult stage, the pupae creep out of the water and attach themselves there at

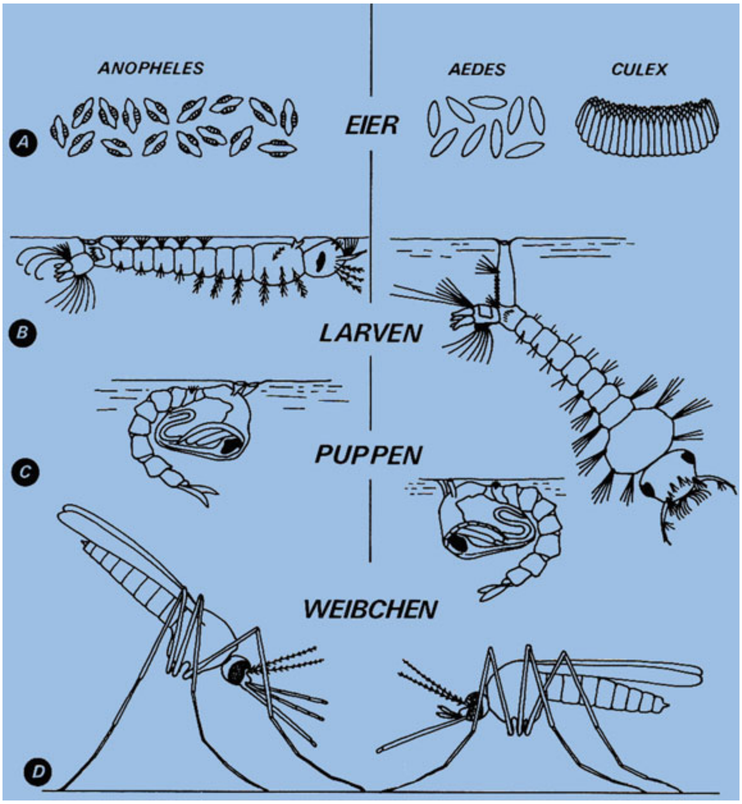


Fig. 5.66 Diagrammatic representation of the life cycle stages of mosquitoes of the genera *Anopheles, Aedes* and *Culex*

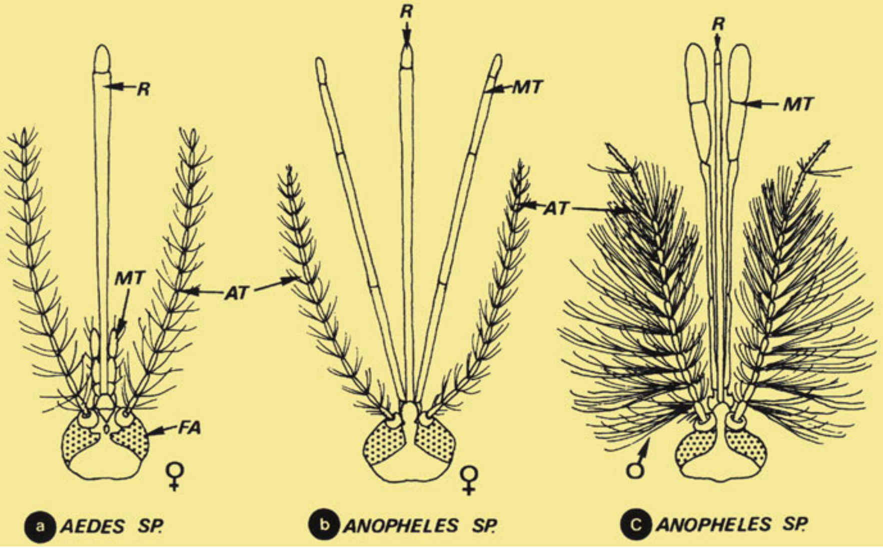
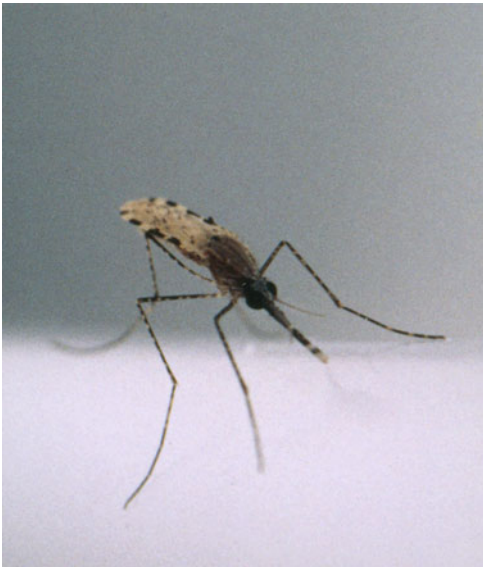

R
MT
AT
FA
♀
a AEDES SP.
R
MT
AT
♀
b ANOPHELES SP.
R
MT
AT
♂
c ANOPHELES SP.

Fig. 5.67 Diagrammatic representation of antennae of *Aedes* and *Anopheles* species. *AT* antennae; *FA* compound eyes; *MT* maxillar palps; *R* labium (sucking channel)

Fig. 5.68 Macroscopical picture of a female *Anopheles stephensi* sucking a sugar solution in the laboratory



plants. Then the fully developed adult stage hatches from the pupal cover and gets dry and stiff within a temperature-dependent short time. The sitting position of the females during blood meals is species specific (Fig. 5.66).

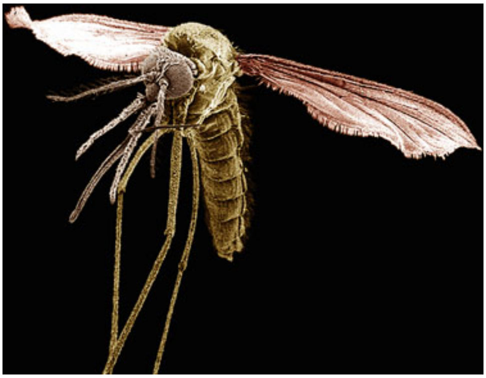


Fig. 5.69 Scanning electron micrograph of a female *Anopheles* mosquito. Note that females have only a few bristles along their antennae

5.5.4.1 Fever Mosquitoes (Genus *Anopheles*)

1. **Name**: Greek: *anopheles* = worthless.
2. **Biology, morphology**: *Anopheles* are able to transmit the agents of human malaria (=*Plasmodium*) in tropical and subtropical regions. However, also some few warm months during a year would be sufficient to establish a malaria epidemic, as it was shown in the seventeenth century or after the First World War (1918) when infected soldiers and/or workers came back to Germany. Transmission, however, depends on the development of the sporozoites inside the female *Anopheles* mosquito and this starts only when at least a whole day-night temperature of 18 °C is given for 14 days. The vectors are worldwide up to 60 *Anopheles* species, which may produce during 10 egg-laying phases up to 2500 eggs. Within a temperature-dependent time of 2–3 weeks, the adult mosquitoes are developed via four stages (instars) of motile larva stages and one motile, but not feeding pupa. Most *Anopheles* species are nightly active (evening and early morning). In moderate regions, they are less aggressive for humans, since they prefer blood of animals. However, in endemic malaria regions they endanger even today millions of humans. In Germany several species occur (e.g. *A. atroparous, A. maculipennis, A. messae*) which fly in a zigzag route and bite mainly during night, while *A. plumbeus* attacks humans and animals during day and night.
3. **Transmission of agents of disease**: Females of the *Anopheles* species are the exclusive vectors of the agents of malaria (*Plasmodium* species; see 3.16). In the region around the Mediterranean Sea, the species *A. labranchiae, A. superpictus* and *A. pharaoensis* occur. In Africa *A. funestus, A. moucheti, A. nili* and *A. gambiae* among others occur. In Eurasian-Asia regions *A. stephensi, A. fluviatilis* and *A. pulcherrinus* are found, while in India and Sri Lanka *A. culicifacies* is one of the dominant species. In South East Asia *A. maculatus* and *A. sundaicus* are found, whereas in South and Central America *A. albimanus, A. pseudopunctipennis, A. bellator, A. cruzi, A. darling* and *A. aquasalis* occur besides A. *nuneztovari*.
4. **Control measurements**: See Chap. 5.6

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5.5.4.2 *Culex-, Culiseta* Species (House Mosquitoes)

1. **Name**: Latin: *culex* = mosquito; *seta* = bristle.
2. **Biology, morphology**: The so-called house mosquitoes of the genera *Culex* and *Culiseta* (*Theobaldia)* are widely known (Figs. 5.66, 5.70), so that their behaviour is—erroneously—often transferred on all bloodsucking mosquitoes. *Culex* specimens are small to middle sized (4–5 mm in length), while *Culiseta* specimens are larger (7 mm). Both species live close to human buildings and the females enter houses and stay therein. The larvae may grow up also even in dirty polluted waters. In Europe, the males die at the end of the summer and only the fertilized females overwinter inside dwellings/stables, etc. In spring time, they leave their winter quarter and start laying eggs of which 15–300 are glued together, thus forming ship-like buildings swimming on the surface of lakes, etc. The cover (called operculum) of the egg is directed to the water surface and opens as soon as the larva is ready to hatch. The development via four larval stages (Fig. 5.66) takes 2–3 weeks; the following pupa stage needs a few days until the first new adults may start propagation. Since in Europe rather warm

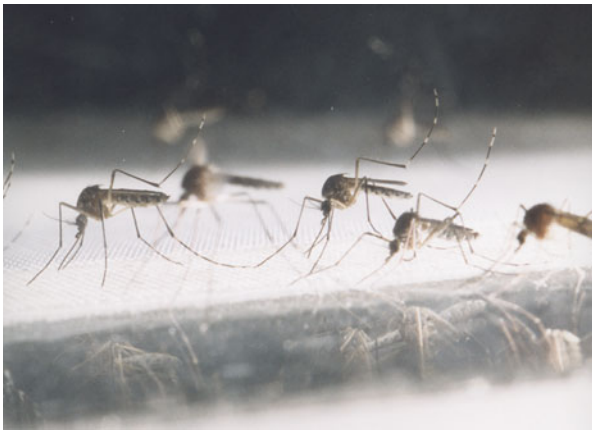

Fig. 5.70 Macrophoto of females of *Culex quinquefasciatus* in laboratory

water is available for the whole summer (and in the tropics for the whole year) many generations will follow each other with giant numbers of bloodsucking females. Thus, control measurements must be done early inside houses and close to houses in order to avoid mass production of mosquitoes during warm periods (Fig. 5.70) as it is the case in the slums of towns in many tropical countries.

3. **Transmission of agents of disease**: While the potential transmission of viruses is common in many countries (but often not noted!), the vectorship for filariae such as *Wuchereria bancrofti* and *Brugia malayi* (Fig. 4.49) is restricted to some regions in Africa, India, Asia and/or South America. The species *Culex pipiens fatigans* is very commonly used as vector (Table 5.6).
4. **Control measurements**: See Chap. 5.6.

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Sudeep AB (2014) *Culex gelidus*: an emerging mosquito vector with potential to transmit multiple virus infections. J Vector Borne Dis 51:251–258.

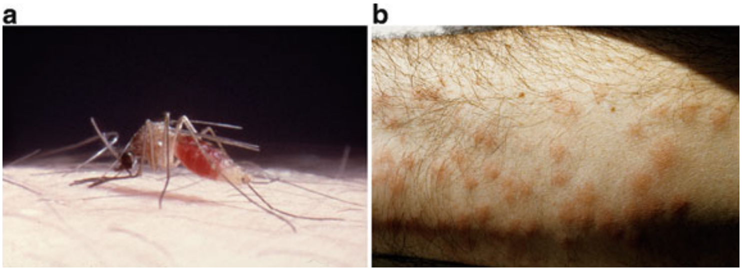
5.5.4.3 *Aedes* Species

1. **Name**: Greek: *aedes* = room, chamber. Latin: *aegyptus* = belonging to Egypt.
2. **Biology, morphology**: The members of this genus run through a very specific life cycle (Figs. 5.66 and 5.71), since they overwinter (in colder regions) only as eggs while in warm regions no phases of rest (diapause) occur and the larvae hatch from the eggs after they had been placed days before at the border of water—they may even develop in small water containers on a terrace or in floodwater after a long rain phase. The females die after they have laid about 100 eggs, which are very resistant against heat, coldness and dryness, so that they may survive up to 3 years, if no water is available or temperatures are too cold. In cold regions, the eggs overwinter and the larvae are produced within 8 days after the temperatures have been increased in spring time, while in warm countries the reproduction is never stopped. After four larval stages (Fig. 5.66) the motile pupa is formed, from which the adults hatch often already 8–12 days after the first larva had left the egg shell. This makes it clear why masses of this

Table 5.6 Important sandfly species as vectors of agents of leishmaniasis (selection)

Sandfly species	*Leishmania* species	Report of occurrence	Grade of vector
Old World			
P. chinensis	*L. infantum*	China	2
P. argentipes	*L. donovani*	India	1
P. perniciosus	*L. aethiopica*	Mediterranean	1
P. pedifer	*L. donovani*	Kenya, Ethiopia	1
P. orientalis	*L. infantum*	Sudan	2
P. longicuspis	*L. tropica*	North Africa	3
P. sergenti	*L. major*	Middle East	1
P. alexandri	*L. major*	North Africa, China	1
P. papatasi	*L. major*	North Africa, Middle East	1
P. martini	*L. donovani*	East Africa	1
New World			
Lu. longipalpis	*L. infantum, L. chagasi*	South/Central America	1
Lu. evansi	*L. infantum*	Colombia	2
Lu. olmeca olmeca	*L. mexicana*	Central America	1
Lu. umbratilis	*L. guyanensis*	Amazon basin	1
Lu. verrucarum	*L. peruviana*	Northern Andes	1
Lu. wellcomei	*L. braziliensis*	Brazil	1
Lu. gomezi	*L. panamensis*	Central America	2
Lu. aracuchensis	*L. peruviana*	Peru	3

Grade of vectors: **1** proven vector. **2** anthropophilic vector, within which parasite stages had been diagnosed. **3** suspected vector. Results according to Lane and Crosskey (1995)
P Phlebotomus, *Lu Lutzomyia*, *L Leishmania*



Figs. 5.71 (**a**) Macrophoto of an *Aedes* mosquito, the abdomen of which is filled by engorged blood. (**b**) Macrophoto of skin reactions after severe bites of *Aedes* mosquitoes

species may occur in water-rich regions and molest humans and animals. In Central Europe, the species *Aedes vexans* (the agonizing one) and *A. sticticus* (the numerous/tight one) are very common and may fly from their breeding sites many kilometres to villages and towns, where they may become serious threats (Fig. 5.71a, b).

3. **Transmission of diseases**: *Aedes aegypti* and other *Aedes* species are important vectors of agents of diseases especially in warm tropical countries. They can be easily recognized by whitish or silver looking scales on their backside forming a lyra-like pattern. These species are able to reproduce even inside smallest amounts of water (after rain) and may be transported easily by buses, cars, etc., into new regions. The females of this species are able to transmit the agents of several important virus-derived diseases:
   - **Yellow fever**: A vaccination is available;
   - **Dengue fever**: The four types endanger up to 1.5 billion humans in Asia, West Pacific, East Africa, Central and South America and lead to more than 20,000 death cases per year. One main vector is *Aedes albopictus*, which was recently introduced even in the rather cold Germany.
   - **Haemorrhagic dengue fever (DHF)**: This variation is especially found in Philippines, Indonesia and other regions in Asia. This fever endangers especially children at ages of 1–13 years causing the highest death toll. After an incubation period of 5–8 days, the first phase of disease starts with fever, abdominal pain and vomiting. During the following days the face swells up and the legs become cold followed by the occurrence of haemorrhages along the skin and mucus layers, nose bleeding and appearance of blood inside vomited fluids or excreted feces.
   - **Japanese encephalitis**: The virus of this disease is transmitted by the so-called bush mosquitoes (*Aedes japonicus*), which was recently "imported" into Germany.

4. **Control measurements**: See Chap. 5.6. While active vaccines exist against the Yellow fever and Japanese encephalitis, they are still lacking and/or under development against the Dengue variations.

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Werner D et al (2015) First record of *Aedes koreicus* (Diptera: Culicidae) in Germany. Parasitol Res. doi:10.1007/s00436-015-4848-6 (epub ahead of print).

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new introduction event and from a split from an existing population. Parasit Vectors 8:40.

5.5.4.4 *Mansonia richiardii*

1. **Name**: The name is derived from the family names of the English scientists Sir Patrick Manson (1844–1922) and the French scientist Richiard.
2. **Biology, morphology**: *M. richiardii* is the only Central Europe species of this genus, which was formerly called *Taeniorhynchus*. The larvae of this species overwinter in plant-crowded freshwaters. Both larvae and pupae obtain their oxygen on a curious pathway. In contrast to other mosquito species, which take up their oxygen at the surface of their water biotope, the specimens of this species do not come to the surface of the water, but enter their breathing pipes into water plants and thus obtain their oxygen. Therefore, they breed exclusively in water sites, which do not fall dry. During autumn the females depone their eggs (united as a little float) onto the surface of their water biotope. The females bite during day and night, but develop in Europe only one generation per year. Since they are as intensely active as the females of the genus *Aedes*, they may become a similar nuisance.

   The most important man-biting species of the subgenus *Mansonia* is *M. titillans*, which occurs in South and Central America as well as in some southern states of the USA. This species is vector of various arboviruses.

   The subgenus *Mansonoides* occurs in the so-called Old World (Africa, India, Japan, Australia). These species also transmit arboviruses, but *M. annulata* and six other species are in addition important vectors of *Brugia bancrofti* in India and South East Africa.
3. **Control measurements**: See Chap. 5.6.

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5.5.4.5 Black Flies (Simuliidae)

1. **Name**: Latin: *simulare* = simulate, feign. Old German: *kriebel* = very small, tiny = Kriebelmücken; Latin: *damnosus* = harmful, damaging.
2. **Biology, morphology**: The small, 4–5 mm long, blackish appearing specimens of this genus look more like flies than as mosquitoes, since their thorax is covered by a hump-like scutum. Also the legs are considerably shorter and thicker than those of true mosquitoes (Figs. 5.72, 5.73, 5.74 and 5.75). The wings are broad and in contrast to mosquitoes they are not covered by fine scales, only the wing “veins” are strongly developed. The two compound eyes appear

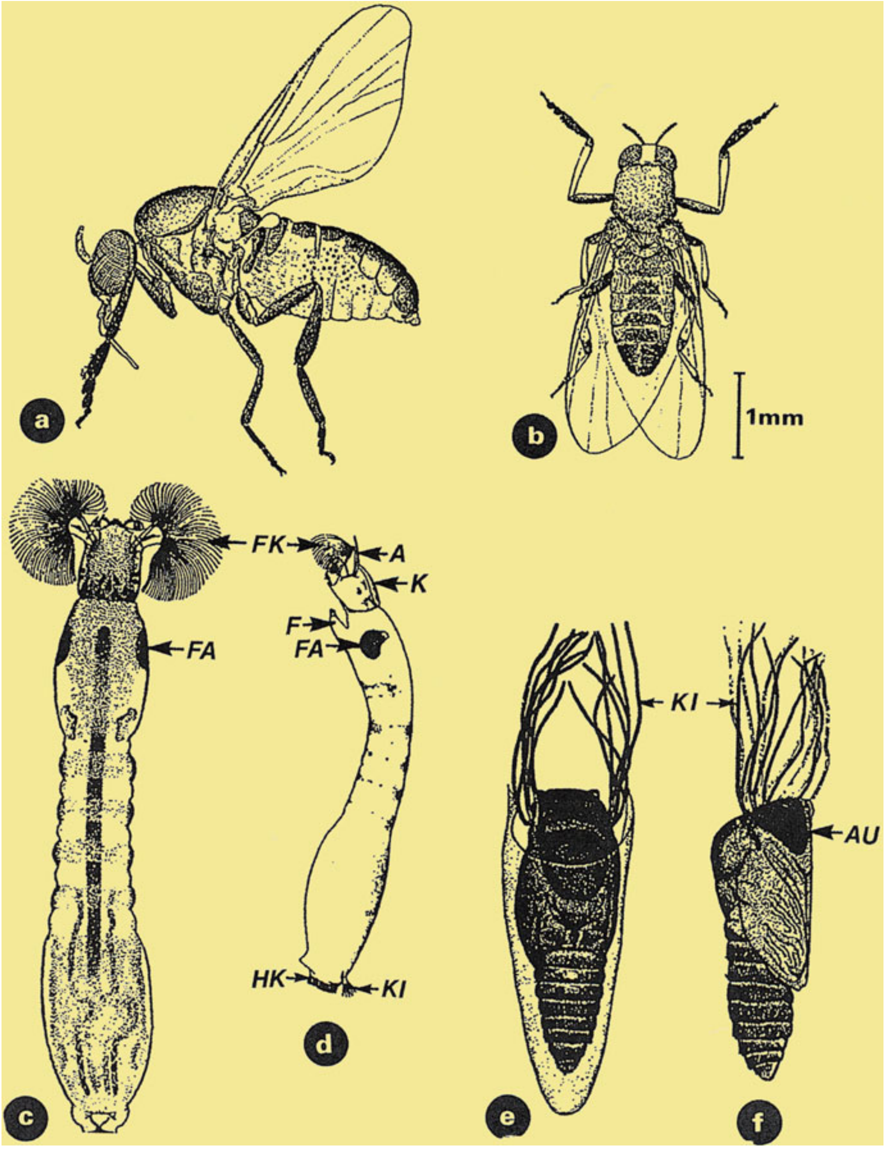

Fig. 5.72 Diagrammatic representation of the developmental stages of black flies (simuliids). (**a**) Adult females. (**c**, **d**) Larval stages: dorsal and lateral aspects. (**e**, **f**) Pupae in their cocoons, lateral and dorsal aspects. The anlagen of the eyes and wings are visible as well as the gills. *A* antennae; *AU* anlage of eyes; *F* small foot; *FA* wing anlage; *FK* filtering protrusions of the head; *H* corona of hooks; *K* head; *KI* gills

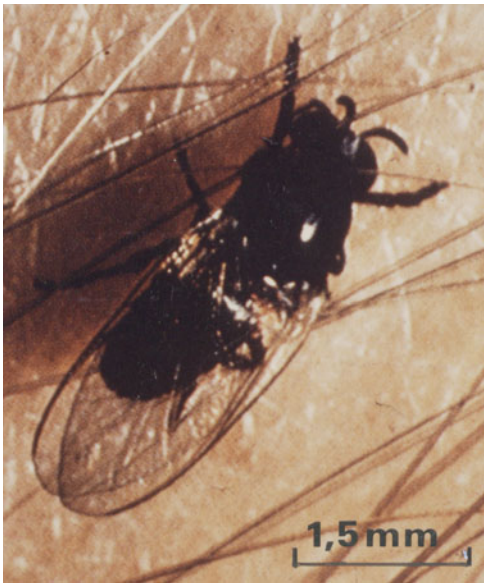

Fig. 5.73 Light micrograph of an adult black fly (*Simulium* sp.)

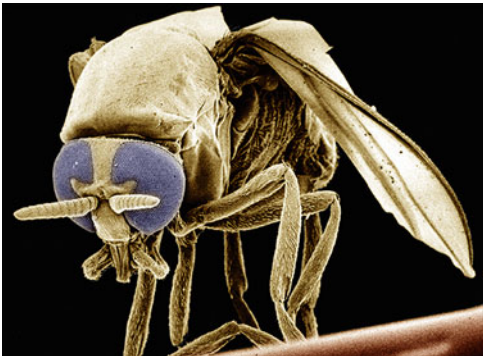

Fig. 5.74 Scanning electron micrograph of a female *Simulium* black fly

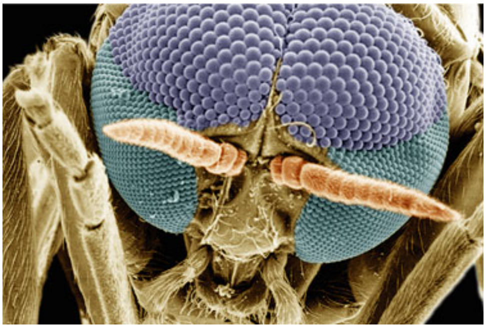

Fig. 5.75 Scanning electron micrograph of the anterior end of the male of a black fly. Note the small and large ommatidia or the compound eye

differently developed in males and females. While the females possess only ommatidia of the same size, the males possess both larger and smaller ommatidia in the eyes (Figs. 5.74, 5.75). The two rather short, horn-like appearing antennae are rather thick and are composed of 9–12 segments (most species, however, have constantly 11 segments). The females suck blood by the help of toothed mandibles and maxillae. However, not all *Simulium* species suck blood. Males never suck blood. Most of the bloodsucking species attack a broad spectrum of vertebrates, while others are specialized on birds or mammalians. There is no species which sucks exclusively at humans; however, there are species, which produce fertile eggs without any blood sucking (=autogenous species).

The simuliids are worldwide distributed—their temperature spectrum reaches from the tropics until subarctic regions where they occur in extremely large numbers. However, their progeny is more or less exclusively developed in quickly flowing waters (Fig. 5.72). Often large masses of specimens occur so that attacked cattle run away in a stampede. Females glue groups of 150–600 eggs at water plants or at stones. The hatched larvae are slender and become fixed at plants or stones by the help of their terminal cuticular hooks and/or by glueing filaments (Figs. 5.72c, d). They get their food by filtering microorganisms by the help of a pair of fan-like structures at their anterior pole. The larvae may change the place by caterpillar-like movements. The larvae grow up via 6–8 stages each being separated by a moult. The last stage is transferred into the typical pupa stage (Figs. 5.72e, f). In Central Europe, 2–3 generations are formed during summer. Overwintering in cold regions occurs at a larval stage, while in the tropics the reproduction cycles are not interrupted.

After hatching from the pupal cocoon, the females start to search hosts close to their breeding sites. Such hosts are attacked exclusively during daytime. The bloodsucking process is rather long, lasts from 4–6 min up to 1 h and is mostly not interrupted, if not disturbed. Their bites are very painful, since simuliids are not **vessel feeders** (as e.g. *Anopheles* mosquitoes, which enter their mouthparts into fine blood vessels), but are **pool feeders**, since their sharp mandibles cut up blood vessels, so that little hollows (pools) are filled by blood (Fig. 5.76).

3. **Bite reaction**: Reactions on bites of simuliids may vary considerably. They reach from slight allergic symptoms to large haemorrhagies after numerous simultaneous attacks. Some persons also suffer from anaphylactic shocks. The bite itself is very painful.
4. **Transmission of agents of disease**: Simuliids transmit neither protozoans nor viruses among humans; however, they may transmit in Africa mechanically bacteria when injecting their potentially contaminated mouthparts. On the other hand, they are vector of the human filarial worm *Onchocerca volvulus*, the larvae of which may induce blindness (see 4.4.19). In Brazil, the species *Simulium amazonicum* transmits the human filarial *Mansonella ozzardi*.
5. **Control measurements**: See Chap. 5.6.

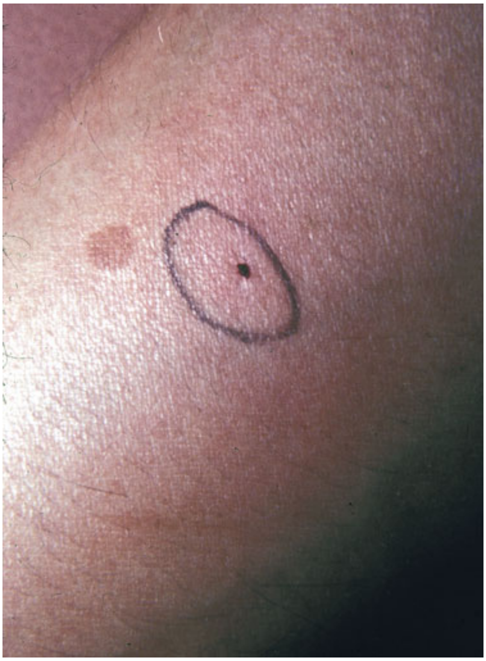

Fig. 5.76 Macrophoto of the bite site of a black fly on human skin

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5.5.4.6 Sandflies (Phlebotomidae) and Moth Flies (Psychodidae)

1. **Name**: Greek: *phleps* = blood vessel, vein; *psyche* = soul.
2. **Biology, morphology**: The families Phlebotomidae and Psychodidae had formerly been kept closely together as single group. However, modern morphological and molecular biological studies showed that they are clearly different:
   - **Psychodidae**: The species of this family are not parasites, are very small, measure only 2–3 mm in length and keep their wings in a roof-like position when sitting on the floor. Their adult stages have very short mouthparts and lick or suck never blood. Their breed lives in water, which must contain a lot of bacteria. For example, their larvae are found very often in toilets, which had not been cleaned for a longer period, feeding on the bacterial flora at the draining away. The typical eggs are placed by the females close to water

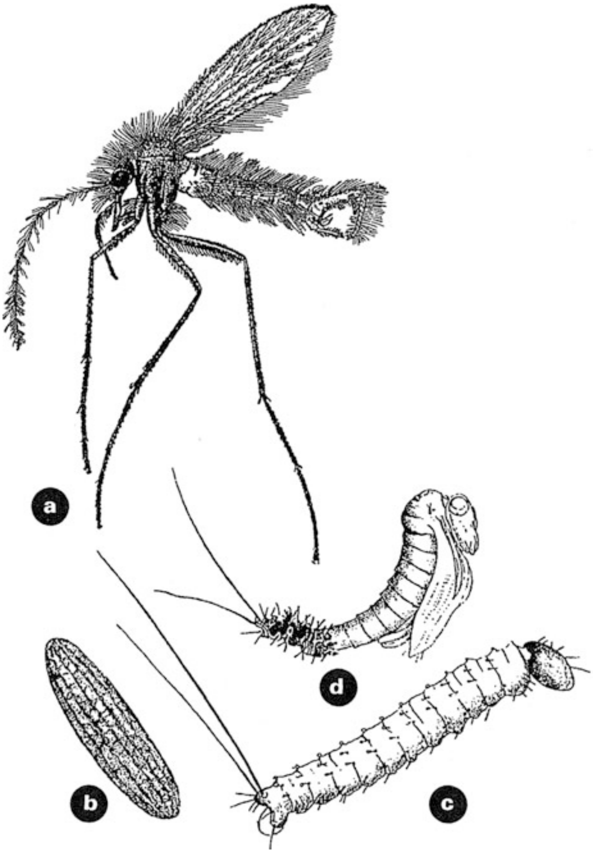

Fig. 5.77 Developmental stages of the sandfly *Phlebotomus papatasi*. (**a**) Lateral aspect of an adult female showing the hair along the body and wings. (**b**) Egg. (**c**) Larva. (**d**) Pupa

surface, where also the pupae (containing a larva) were found. Due to their very small size, they had been confused with the sandflies in regions, where both groups occur.

- **Phlebotomidae**: The specimens of this group measure about 4 mm in length, possess strong bloodsucking mouthparts and bear their wings angel-like (Figs. 5.77 and 5.78). Their wings show much less hair than those of the Psychodidae and also the strong anal vein of the psychodid wing is absent. While the psychodids occur worldwide in very different climates, the phlebotomids are found mainly in the subtropics or in the tropics. However, only 3 genera of the 24 described phlebotomids are of medical importance: *Phlebotomus* and *Sergentomyia* in the "Old World" and *Lutzomyia* in America.

Breeding sites are caves, soil caverns, rubbish heaps, nests of rodents and lizards, which have to be dark, humid and warm, but should never be wet. In Europe, railway tunnels or indoor sleeping places of bats are common resting

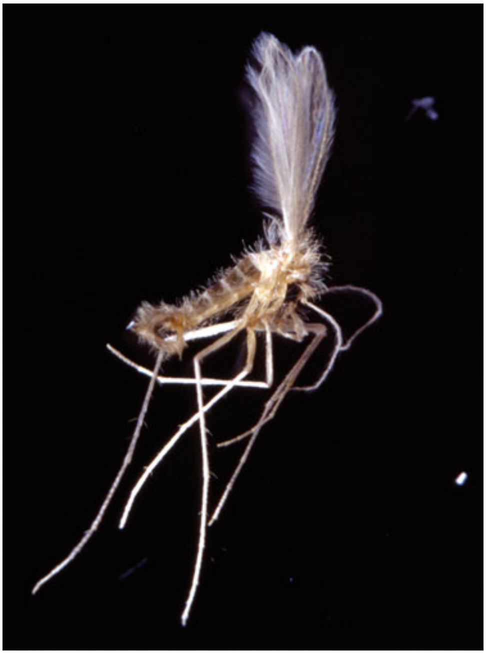

Fig. 5.78 Light micrograph of a female stage of *Phlebotomus papatasi*

places for phlebotomids. The phlebotomid larvae (in general occur four stages, which feed disintegrating organic material inclusive remnants of insects, fecal particles, etc.) develop very often close to slums in tropical regions, if they are not killed during campaigns to eliminate the vectors of malaria.

The individual speed of the development via 4 larval stages and a pupa to the adult stage depends on the temperature. About 100 days are needed at a temperature of 18–20 °C, while at temperatures around 28 °C only 50 days are needed. As in the case of mosquitoes only the females of the sandflies (Figs. 5.77 and 5.78) suck blood. Bloodsucking activity starts in the early evening hours and lasts through the whole night, while they hide themselves during daytime at dark places. They are especially active during warm, humid and calm nights. Blood sucking mainly occurs close to the hiding places (~ at a radius of 1 km at the maximum) and very often they live inside houses or nearby.

Host specifity is low. However, humans are attacked only by a few species (Table 5.6). Many of them prefer rodents, dogs or even reptiles as blood donors. *Phlebotomus papatasi* which is very important in South Europe as vector of the agent of the leishmaniasis has two main activity phases: June and August until the end of September.

3. **Biting reactions**: The bites occur at places with a smooth skin, e.g. in the face, neck, at hands and in the regions of the ankles. They are rather painful since the mouthparts of these insects are rough and hollow inside the skin, which is filled by the blood of destroyed blood vessels.

4. **Transmission of agents of diseases**: The bloodsucking females of the sandflies are vectors of very important diseases of humans. They are, e.g., vectors of
   - ***Bartonella bacilliformis***. This bacterium is in Peru and Columbia the agent of the so-called **Oroya fever** (*engl.* Carrions disease). If patients survive the first signs of this disease, a skin disease named **Verruga peruana** is developed.
   - Viruses transmitted in Egypt and Eurasia until India may induce the so-called **Pappataci fever**, which is also called **3-days fever** or **dog's fever**. The viruses become apparently included into the mosquito eggs, so that also the next generation is infected.
   - Among other transmitted parasites, the protozoans of the genus *Leishmania* are very important (see Chap. 3.7).
5. **Control measurements**: See Chap. 5.6.

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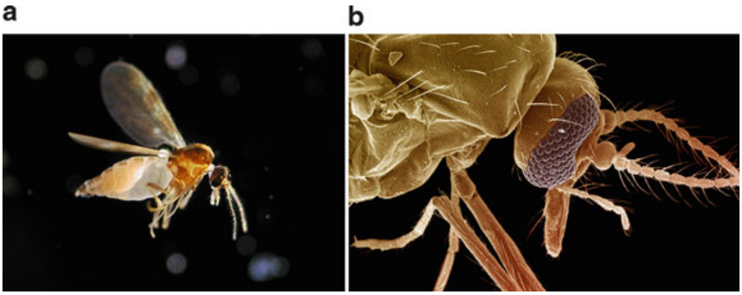
5.5.4.7 Midges (Ceratopogonids)

1. **Name**: Greek: *keras* = horn; *pogon* = beard. English: *biting midges*. North American: *punkies*. African: no-seeums = they are not observable; German: Gnitzen.
2. **Biology, morphology**: About 50 genera occur worldwide; however, only four of them are of medical or veterinarian importance. The adults are very small and measure from 0.8 mm up to 4.5 mm in length (Figs. 5.79, 5.80). In the different species of the four genera *Culicoides*, *Leptoconops, Forcipomyia* and *Austroconops*, the females are able to transmit agents of disease to their vertebrate hosts.

   The larvae (Fig. 5.80) live in/on humid soil which contains remnants of plants. These conditions are given close to freshwater lakes and especially in stables of cattle, etc. There are also species, where larvae live inside pits at the base of leaves; others are even found inside brackish water. In the case of the bloodsucking species, **only** the **females** suck blood using their short but strong mandibles (Fig. 5.79b), which cut the skin, thus forming little blood-filled pools. Therefore, they belong to the pool feeder group (like black flies, tabanids) and not to the vessel feeder such as mosquitoes, which inject their mouthparts into the blood vessels without disrupting them. The bites of these specimens are very



Figs. 5.79 (**a**) Light micrograph of a female of the midge species *Culicoides obsoletus*, vector of the blue tongue virus. (**b**) Scanning electron micrograph of the head of a female of the species *Culicoides obsoletus*. Note the stiff mandibles, the compound eye and the two antennae

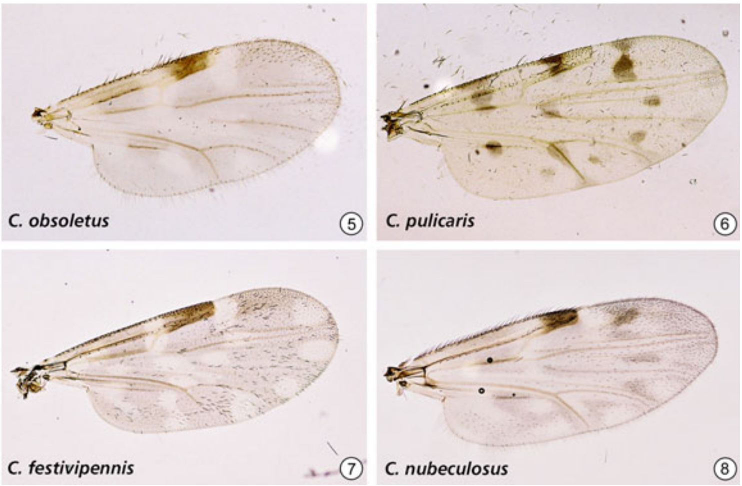


Fig. 5.80 Wings of important *Culicoides* species

painful and lead to an intense feeling of burning. Most species start blood sucking during dusk. Since their bite reactions are painful and due to the fact that they are hardly seen, Africans call them “no-seeums”. The genus *Culicoides* contains about 800 species, which produces often extremely high numbers of specimens. They are diagnosed by their typical wings and by the fact that they keep their wings attached to the abdomen when sitting (Fig. 5.80b). The action radius of these bloodsucking midges is rather narrow, since they remain close to their hosts. However, due to their small size they may easily become drifted away even by low-grade winds, which is important in cases where agents of disease are contained inside their salivary glands. Apart from mammalians, midges also attack birds. In any case, masses of these blood suckers may become a severe nuisance.

Table 5.7 Selected agents of diseases transmitted by midges of the genus *Culicoides*

Agents of disease	Main hosts	Distribution/Endemic regions
Dipetalonema perstans (**N**)	Humans	Africa, South America
Dipetalonema streptocerca (**N**)	Humans	West/Central Africa
Haemoproteus species (**P**)	Birds, reptiles	Worldwide
Hepatocystis species (**P**)	Monkeys, bats	Africa
Blue tongue virus (**V**)	Ruminants	Worldwide
Akabane virus (**V**)	Cattle	Australia, Japan
African horse death virus (**V**)	Horses	Africa, cases in Europe

N Nematodes; *P* Protozoa; *V* Viruses

The genus *Forcipomyia* (subgenus *Lasiohelea*) contains about 50 species, which mainly occur in warm countries. They include day-active species. The Australian species *Austroconops macmillani* is the only species, which occurs in Western Australia and attacks humans during daytime. It prefers biting sites around the eyes. The bites are painful and induce considerable swellings for up to 3 days.

3. **Transmission of agents of disease**: The importance of midges as vectors of agents of diseases was not noticed for long since they are mostly not seen. However, the last 10 years have shown that they are important vectors of agents of diseases. Especially endemics due to infections of cattle with blue tongue viruses or horses with those of the so-called horse sickness are commonly known. For example, an epidemic with the blue tongue virus serotype 8 occurred in Europe in the years 2006–2010 killing 4–40 % of the infected sheep and cattle until a vaccine became available. Since alone 24 serotypes occur belonging to the blue tongue virus, it can easily be estimated how quick epidemics may arise. Midges are also able to transmit the larvae of filarial worms, which, however, have no importance for humans.
4. **Control measurements**: See Chap. 5.6 (Table 5.7).

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Schmahl G et al (2009) Pilot study on deltamethrin treatment (Butox®7.5, Versatrine®) of cattle and sheep against midges (*Culicoides* species, Ceratopogonidae). Parasitol Res 104:809–813.

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5.5.5 Flies (Brachycera)

1. **Name**: Old German: *fliugan* = flying. Greek: *brachys* = short; *keas* = horn. French: mouches.

5.5.5.1 Snipe flies (*Rhagionidae*)

1. **Name**: Greek: *rhagion, rhax* = berry.
2. **Biology, morphology**: Specimens of several species of the Rhagionidae bite humans. Especially members of the genus *Symphoromyia*, which occur in Eurasia and in America, land softly on human skin, before they start with their painful biting activity. The genus *Atheris* occurs in North and South America, while in Australia the genera *Austroleptis* and *Spaniopsis* are known as true nuisances.

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5.5.5.2 Louse Flies (*Hippoboscidae*)

1. **Name**: Greek: *hippos* = horse. Latin: *bos* = cattle. English: *keds*.
2. **Biology, morphology**: The louse flies got their trivial name, since they live—attached like lice—inside the body hair of their hosts. Their body is strong and their legs are each equipped with two claws which make it possible to become firmly anchored at the surface of their hosts. The wings of the different species are often more or less reduced; their mouthparts are of the biting-sucking type. The louse fly females do not lay eggs but depone larvae just prior to pupa formation. The horse louse fly *Hippobosca equina* and its counterpart from camels *H. camelina* possess wings. Males of *Lipoptena cervi* (stag louse fly, roe deer fly) keep their wings flat, while females detach their wing as soon as they have reached their host (Fig. 5.81). The worldwide distributed species *Pseudolynchia maura* and *P. canariensis* are mainly parasites of doves and related species. They possess wings and thus their local propagation needs only a very short time after they have arrived in a biotope. *Melophagus ovinus* occurs on sheep and was erroneously described in former times as “sheep tick”.

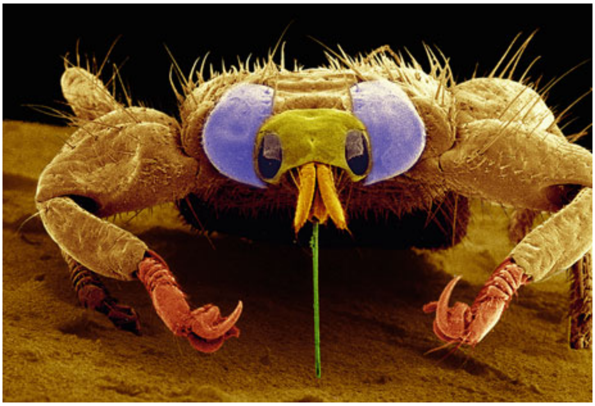

Fig. 5.81 Scanning electron micrograph of *Lipoptena cervi*. Note the large claws and the spiky sucking tube

This species has no wings and thus becomes exclusively distributed during body contacts. The mature pupae are glued by the females at the hair of their hosts, so that they cannot drop to the soil. All these species may also attack humans, if they get in contact with infested animals. The bite of the specimens of this louse fly species is especially painful as well as the skin scratching of their claws.

3. **Control measurements**: See Chap. 5.6.

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Small RW (2015) A review of *Melophagus ovinus*. Vet Parasitol 130:141–155.

Zhang D et al (2015) Ultrastructural investigation of antennae in three cutaneous myiasis flies: *Melophagus ovinus*, *Hippobosca equina* and *Hippobosca longipennis* (Diptera: Hippoboscidae). Parasitol Res 114:1887–1896.

5.5.5.3 Tsetse Flies (*Glossinidae*)

1. **Name**: Tswana: *tsetse* = word imitating the wing sound during motion. Latin: *glossa* = tongue; *morsitans* = killing, biting.
2. **Biology, morphology**: The tsetse flies are very often considered as subfamily of the Muscidae or as genus of the Stomoxynae (biting flies). All existing species belong to the genus *Glossina*, which exclusively occurs in tropical and subtropical regions in Africa between 5° north and 20° south of the equator. These biting flies are easily recognized by the help of several characteristics: Their tongue-like wings are kept flat above the abdomen and the so-called arista at the antenna shows bristles only along its upper side (Figs. 5.82 and 5.83). Tsetse flies do not lay eggs, but produce a single larva, which is deponed in a prepupal stage onto a

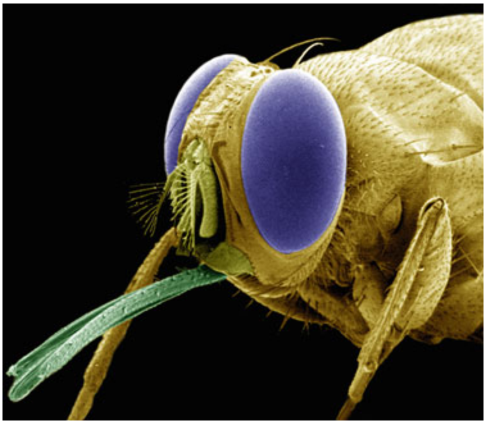

Fig. 5.82 Scanning electron micrograph of the anterior end of a tsetse fly (*Glossina morsitans*)

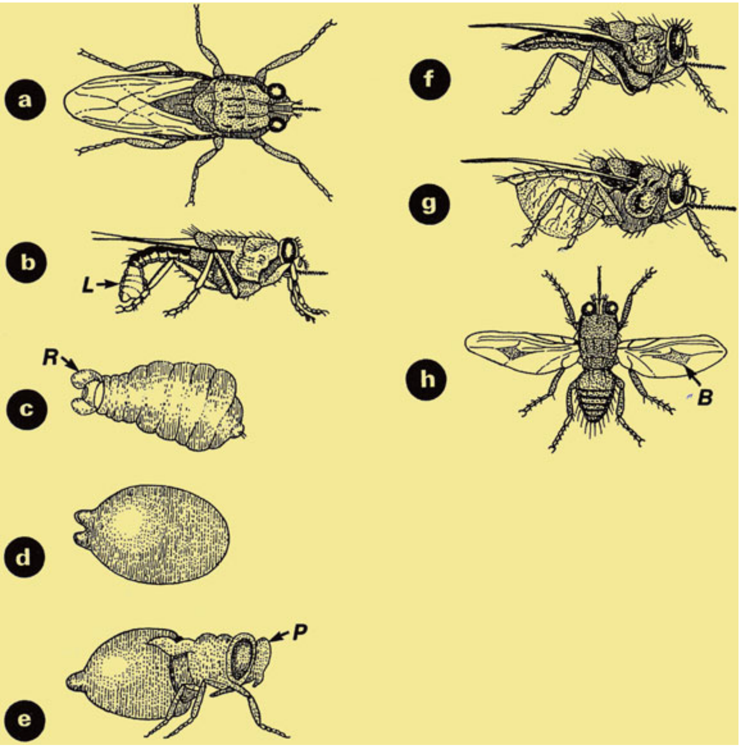

Fig. 5.83 Diagrammatic representation of the developmental stages of the tsetse fly (*Glossina* sp.). (**a**) Adult fly. (**b**) Female deponing the late larva (L). (**c**) Freshly deponed larva with respiratory protrusions®; this stage enters the soil. (**d**) Pupa 2 h after entering the soil the larval cover is hardened and thus becomes the pupal cover. (**e**) Hatching from the pupal cover by the help of a so-called ptilinium. (**f**, **g**) Appearance before and after blood meal; up to 5 amounts of their own body weight may be ingested. (**h**) In the wing a typical field (B) can be seen, which lacks other flies

humid environment (Fig. 5.83). Glossinidae mostly stay close to their hosts, although they have an excellent ability to fly.

3. **Transmission of agents of disease**: The tsetse flies are able to transmit the agents of the Human sleeping sickness and the Nagana of animals (*Trypanosoma* species); see Chap. 3.5.
4. **Control measurements**: See Chap. 5.6.

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5.5.5.4 Typical Flies (Muscidae)

The family Muscidae includes species, where the adults possess either typical licking mouthparts (so-called labella) or bloodsucking, piercing ones. Some species belonging to any of the two groups are of medical importance due to their ability to transport and transmit agents of diseases (such as viruses, bacteria, protozoans or even worm eggs).

Further Reading

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House Fly (*Musca domestica*)

1. **Name**: Latin: *Musca* = fly; *domesticus* = belonging to the house.

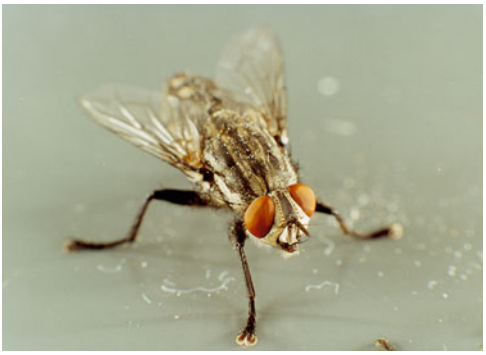

Fig. 5.84 *Musca domestica*. (**a**) Macrophoto of an adult female. (**b**) Scanning electron micrograph of the labella of the fly showing large fields of deepenings filled by saliva, thus allowing to lick up food particles

2. **Biology, morphology**: Adult females of *Musca domestica* (Fig. 5.84) measure 7–8 mm in length; the males are somewhat smaller. The females depone about 2000 eggs, e.g., on feces of house animals (dogs) and farm animals (cattle, horse, etc.), but also onto human feces. The typical apod larva 1 hatches from the egg in a temperature-dependent timing and via 2 moults the typical pupa stage is formed. The whitish larvae have a length of 6–12 mm and feed in general fecal or organic material. Such larvae may enter the gastrointestinal system of animals or even of humans and live there as parasites. After a temperature-dependant period the last larva becomes the pupal stage. Hatching of the adult fly from the barrel-like appearing pupal cover occurs by cutting a circular slit. The whole time needed for the development of the adult fly takes 8–50 days depending on the temperature.
3. **Transmission of agents of disease**: Since the adults of this species lick at feces but also at suppurating wounds, they are able to transmit huge amounts of bacteria, parasites or even viruses (e.g. agents of poliomyelitis, typhus, cholera, salmonellosis, worm eggs, amoebic cysts, etc.) Investigations of Förster et al (2012), Gestmann et al (2012) and Mehlhorn (2012) showed that more than 100 species of agents of diseases can be found on the mouthparts and in the intestine of *M. domestica*. Among them had been many strains of *Escherichia coli* bacteria (e.g. EHEC, EPEC), which have the potential to induce severe epidemics among close together living humans.

   A peculiar disease is the so-called **Egyptian eye disease** (trachoma), which is induced by the bacterium *Chlamydia trachomatis*. This disease IS widespread in southern and eastern countries along the Mediterranean Sea and in Africa, in wide regions of Asia and in South America. It is estimated that about 500 million of humans are infected worldwide. In many cases, this disease leads to blindness. **Transmission**: Most common is the transmission by flies; however, also indirect transmission may occur by common use of towels. **Diagnosis** can be done by the help of smear preparations examined in a fluorescence microscope after treatment with antibodies. **Treatment** must be done by the use of antibiotic compounds dropped into the eyelids.

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Stable Fly (*Stomoxys calcitrans*)

1. **Name**: Greek: *stomoxys* = pointed mouth. Latin: *calcitrare* = step down by help of feet.
2. **Biology, morphology**: The adults measure about 5–7 mm in length and look similar to *Musca*; however, they possess bloodsucking, biting mouthparts (Fig. 5.85). The development from the egg to the adult stage takes about 27–37 days after the female has deponed a total of about 60–100 eggs on fecal material in stables. The females live for about 70 days. In contrast to the mosquitoes, **both sexes of the stable flies suck blood**. Therefore, adults are important vectors of agents of disease such as those of anthrax and infectious anaemia.
3. **Control measurements**: See Chap. 5.6.

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Cruz-Vazques C et al (2015) Efficacy of the entomophathogenic fungi *Metarhizium anisopliae* in the control of infestation by stable flies *Stomoxys calcitrans* (L.) under natural infestation conditions. Vet Parasitol 212:350–355.

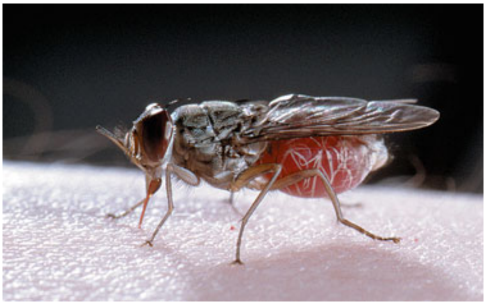

Fig. 5.85 Macrophoto of an adult stage of the stable fly species *Stomoxys calcitrans* on the skin of a host. Note that abdomen appears red due to the ingested blood

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5.5.5.5 Grey Flesh Fly (*Sarcophaga* species)

1. **Name**: Greek: *kallos* = beautiful; *phorein* = carry; *myia* = mosquito, fly; Latin: *carnaria* = belonging to flesh.
2. **Biology, morphology**: The different species (e.g. *S. carnaria*) are rather large reaching a size of up to 16 mm (Fig. 5.86). The females depone at dead or long time immobile bodies (e.g. of animals and humans) the small larvae 1. The larvae may enter the body openings (nose, anus) and lead to the disease called **myiasis**. Adults may be mechanical transmitters of viruses, bacteria and parasitic stages (cysts, eggs).
3. **Control measurements**: See Chap. 5.6.

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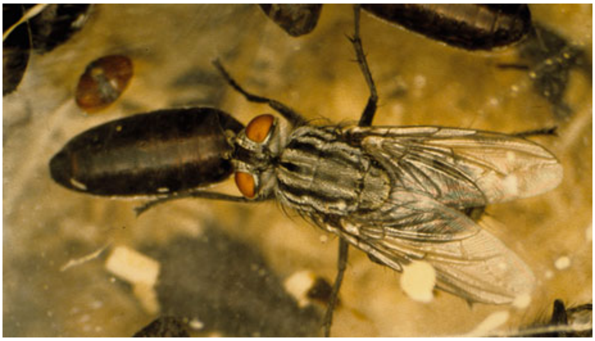

Fig. 5.86 Macrophoto of an adult *Sarcophaga* fly and a pupa

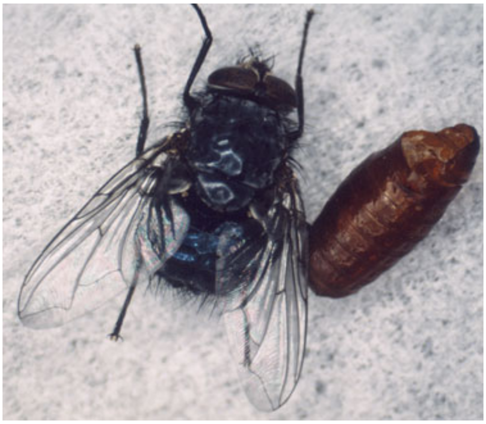

Fig. 5.87 Macrophoto of an adult fly of *Calliphora* sp. and of the pupa

5.5.5.6 Blue Flesh Fly (*Calliphora* species)

1. **Name**: Greek: *kallos, phorein* = bearing.
2. **Biology, morphology**: These flies reach as adults 10–14 mm in length and the females depone their 10,000 eggs in general at dead bodies (Fig. 5.87). They may enter dead bodies, but also enter wounds, thus introducing a myiasis.
3. **Control measurements**: See Chap. 5.6.

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5.5.5.7 Green Flesh (Bottle) Fly (*Lucilia* Species)

1. **Name**: Latin: *lucidus* = shiny; *lux* = light; *cilum* = bristle; *serrare* = tattered.
2. **Biology, morphology**: The different species of this genus (e.g. *L. sericata, L. caesar*, *L. cuprina*, etc.) are also called gold flies, since they appear golden green or blue greenish. The females depone very often their eggs on sleeping persons (into nose, ears) or in open wounds (Fig. 5.88). The adults are rather large: *L. sericata* (5–10 mm) and *L. cuprina* (5–14 mm). The hatching larvae may introduce severe damages, which may even lead to death due to sepsis. “Sterile” living maggots are used to clean non-healing wounds. This efficacy

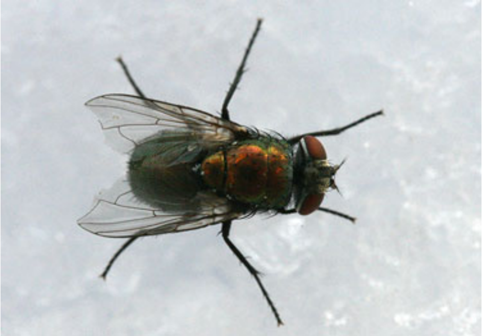

Fig. 5.88 Macrophoto of *Lucilia sericata*. (**a**) Eggs. (**b**) Larva 3. (**c**) Pupa. (**d**) Adult fly

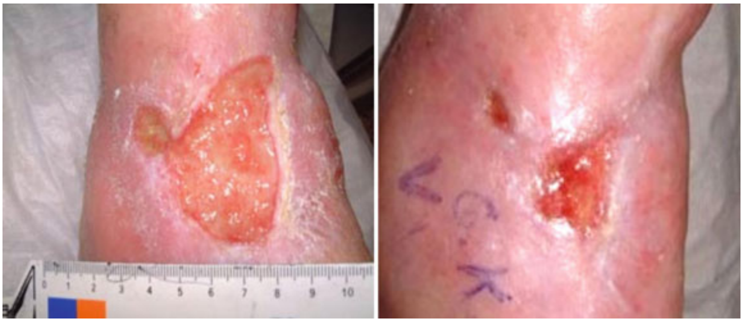

Fig. 5.89 Wounds before and after covering with extracts from *L. sericata*

was already seen in the seventeenth century, when soldiers had been hit by swords and maggots settled inside deep wounds. The company Alpha-Biocare, Germany, produces an extract from those "sterile" maggots, which is used to decontaminate wounds settled by multiresistant bacteria (Larveel® for humans, Larvalin® for animals) (Fig. 5.89).

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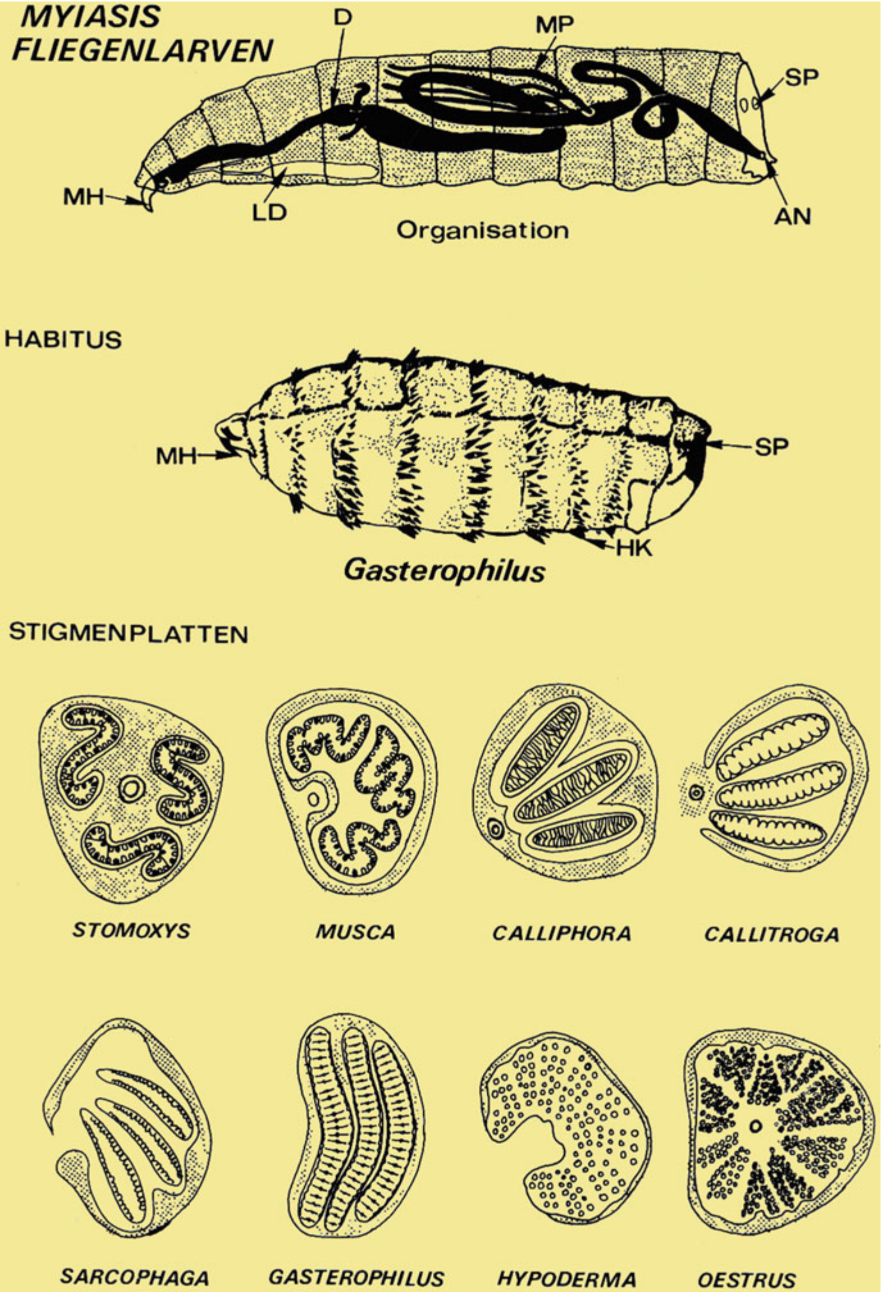
5.5.5.8 Myiasis

1. **Name**: Greek: *myia* = mosquito; however, the name was also used for flies.
2. **Biology, morphology**: The larvae of some cyclorrhaph flies may parasitize as stationary agents of disease in the skin and/or other organs (Figs. 5.90, 5.91). Such an infestation is generally termed **myiasis** and is found along the **skin**, in open **wounds**, in **eyes** and along inner mucosal layers (inside nose, throat, anus, etc.). Furthermore, such parasitizing larvae may be found in the stomach, intestine and in the urogenital system. The females depone either eggs or even already freshly hatched larvae. Thus there exist **larviparous species** and **oviparous** species. The larvae 1 enter the skin or body hollows and leave them, when they have arrived the third larval stage just prior to the formation of the pupa (Fig. 5.91).

   The stationary parasitic larvae appear in different shapes; while larvae 1 and 3 appear sausage like, the larva 2 has a thinner anterior end (Fig. 5.91b), where the retrudable head is situated being characterized by two remnants of the antennae and two hook-like mouthparts, which are used to fix the larva at the bottom of the wound. The somewhat flattened terminal end of the larva bears a pair of the genus--specific spiracles (=stigmata) (Fig. 5.90). *Dermatobia hominis* (human bot fly), which occurs in South and Central America, does not attack its vertebrate hosts (animals, humans) but glues its eggs in bundles of up to 100 (!) at the abdomen of bloodsucking insects like mosquitoes. As soon as these blood suckers take a touchdown at the skin of a human, the larvae (0.5 mm) hatch from the egg and penetrate immediately into the human skin. This peculiar pathway of infection is described as **phoresis** and helps considerably to distribute the progeny of this fly within a large biotope. Inside at the beginning skin tube the fly larva may grow up reaching a length of up to 2.5 cm prior to dropping to the soil, where pupation occurs. In contrast to the larvae of *Hypoderma* species, which migrate within the skin, *D. hominis* larvae remain within their entrance site at the skin.
3. **Treatment**: The larvae of *D. hominis* can be rather easily removed from their “bore hollow”. During squeezing of the wound site the abdominal body portion will appear at the surface of the human skin and can be removed by the help of twisters. However, in most cases bacterial superinfections occur, which must be treated by the help of antibiotic after removal of the larva.
4. **Control measurements**: It is important to keep the number of flies low close to human dwellings. The method of choice is the use of products that block the larval development by spraying growth inhibitors on potential fly breeding sites. For *Musca domestica*, *M. autumnalis, Stomoxys calcitrans* and *Haematobia irritans* several growth regulators are available (e.g. cyromazine, diflubenzuron, methoprene) among several others which have to be used in combination. The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STOMOXYS
MUSCA
CALLIPHORA
CALLITROGA
SARCOPHAGA
GASTEROPHILUS
HYPODERMA
OESTRUS

Fig. 5.90 Diagrammatic representation of fly larvae, which may induce **myiasis** in humans and animals. At their terminal species-specific openings (stigmata, stigma plate) occur, which let enter oxygen. *AN* anus; *D* intestine; *HK* hooks; *LD* labial glands; *MH* mouth hooks; *MP* Malpighian tubes; *SP* stigma plate = opening of the breathing system

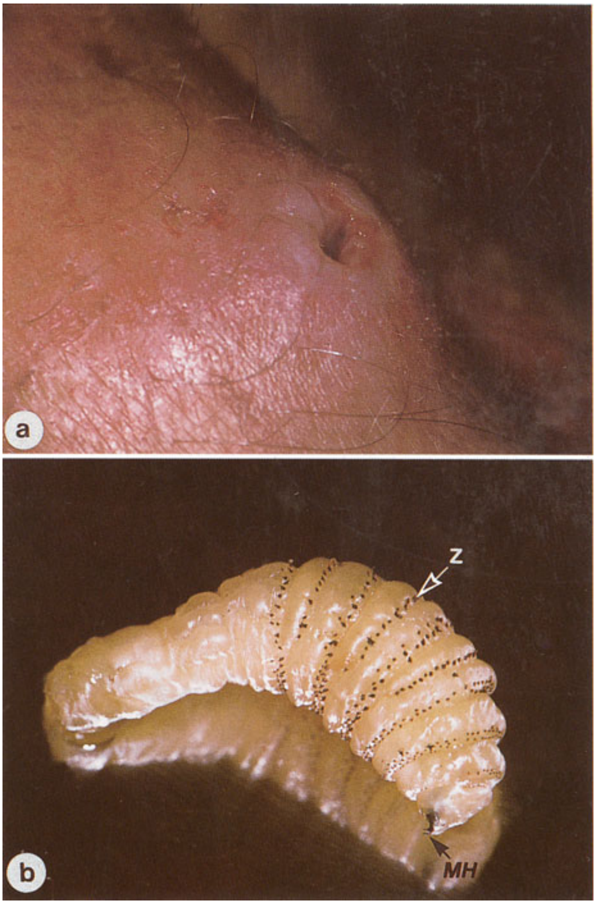

Fig. 5.91 Myiasis due to *Dermatobia hominis*. (**a**) Inflamed hollows inside the skin, wherein the larva lives. The two spiracles at the terminal pole become visible from time to time or when the skin protrusion is pressed by the help of two fingers. (**b**) Larva 2 after chirurgical removal from the wound shown in (**a**). *MH* mouth hooks; *Z* teeth at segment borders. They are used to become firmly fixed inside the wound channel. Note that the anterior end of the larva 2 is tapered (the anterior pole of the larvae 1 and 3, however, are rounded)

"good old glueing fly catcher" inside dwellings in addition to fly nets before the open windows protects very well even in our chemical century.

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5.5.6 Horse Flies (Tabanidae)

1. **Name**: Latin: *tabanus* = stinger; Greek: *haematopota* = drinking blood; Greek: *chrysos* = gold; German: Bremsen (Fig. 5.91).
2. **Biology, morphology**: Horse flies are huge, measuring 5–25 mm in size. They have strikingly coloured eyes and fly rapidly. As in other groups also here only the females suck blood. Their piercing mouthparts are very strong so that their stings can be very painful (Figs. 5.92 and 5.93). More than 3000 species occur worldwide. Humans are affected only by three genera (Fig. 5.94):
   (a) ***Tabanus***, the original horse fly with glossy wings and eyes either transversely banded or uniquely coloured.
   (b) ***Haematopota*** (some authors name this genus as *Chrysozona*), the so-called legs or stouts showing spotted wings and coloured eyes, their colour forming a zigzag pattern (Fig. 5.93).
   (c) ***Chrysops***, the so-called deer flies, appears golden green and possesses wings with a wide tinted band and showing a spotted eye coloration (Fig. 5.95). The blood thirsty females may attack rapidly and aggressively, thus becoming often a pledge for humans and cattle. They even can chase and attack humans riding a bicycle or a horse a.s.o. The larvae develop in muddy parts of channels, ponds, lakes or rivers.
3. **Transmission of agents of disease**: Transport hosts such as Tabanidae may distribute and even transmit pathogens of anthrax and anaplasmosis mechanically on humans by means of their labella when carrying remnants of blood. Ticks and horse flies may distribute tularemia in Europe, Northern Asia and North America. This disease is induced by the bacterium *Francisella* (=*Pasteurella*) *tularensis*. The important vector of this bacterium is the tabanid *Chrysops discalis* in the USA. *Chrysops* species are also vectors of the filarial worm (*Loa loa*) of humans in Africa (Fig. 4.51).
4. **Control measurements**: See Chap. 5.6.

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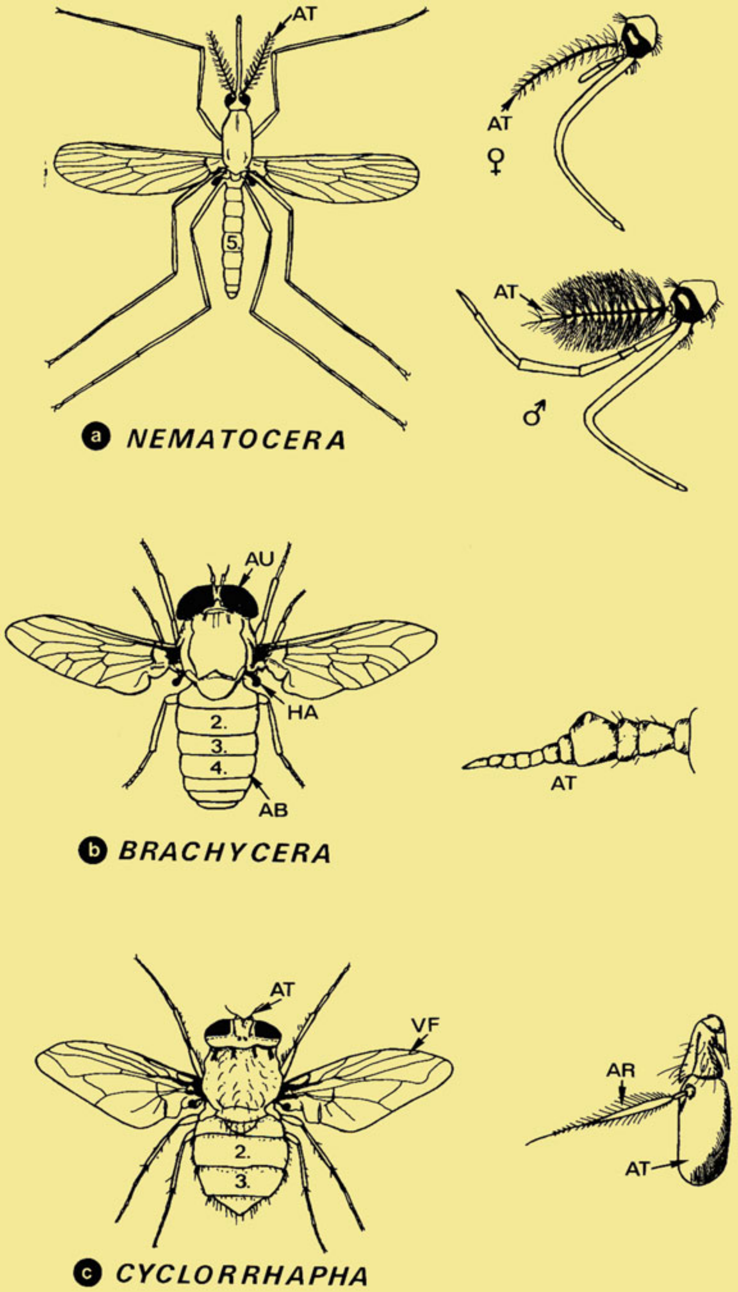
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Fig. 5.92 Diagrammatic representation of mosquitoes (Nematocera), tabanids (Brachycera) and flies (Cyclorrhapha) with their typical antennae. *AB* abdomen; *AR* arista; *AT* antennae; *AU* eye; *HA* halters; *VF* anterior wing

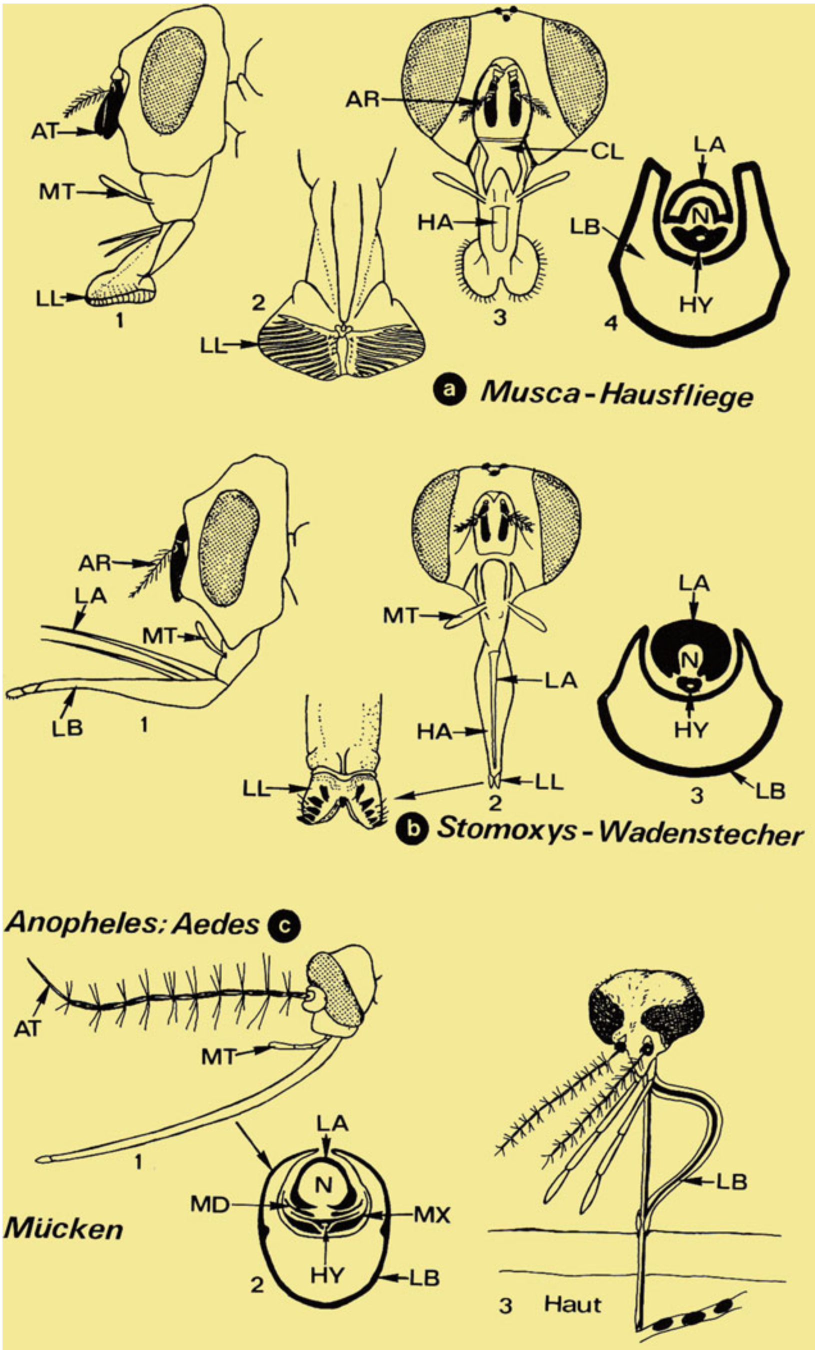
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Fig. 5.93 Diagrammatic representation of the different mouthparts (MW) of diptera. (**a**) **Licking-sucking mouthparts of a fly**: (**1**) lateral aspect of the head; (**2**) Labellum (lip). (**3**) Front view of the head with its huge ommatidia occurring at its forehead (ocelli). (**4**) Cross section through the mouthparts. (**b**) **Piercing-sucking mouthparts of a fly**: (**1**) head, side view. (**2**) Head head-on. (**3**)

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5.6 Protection from Insect Infestation

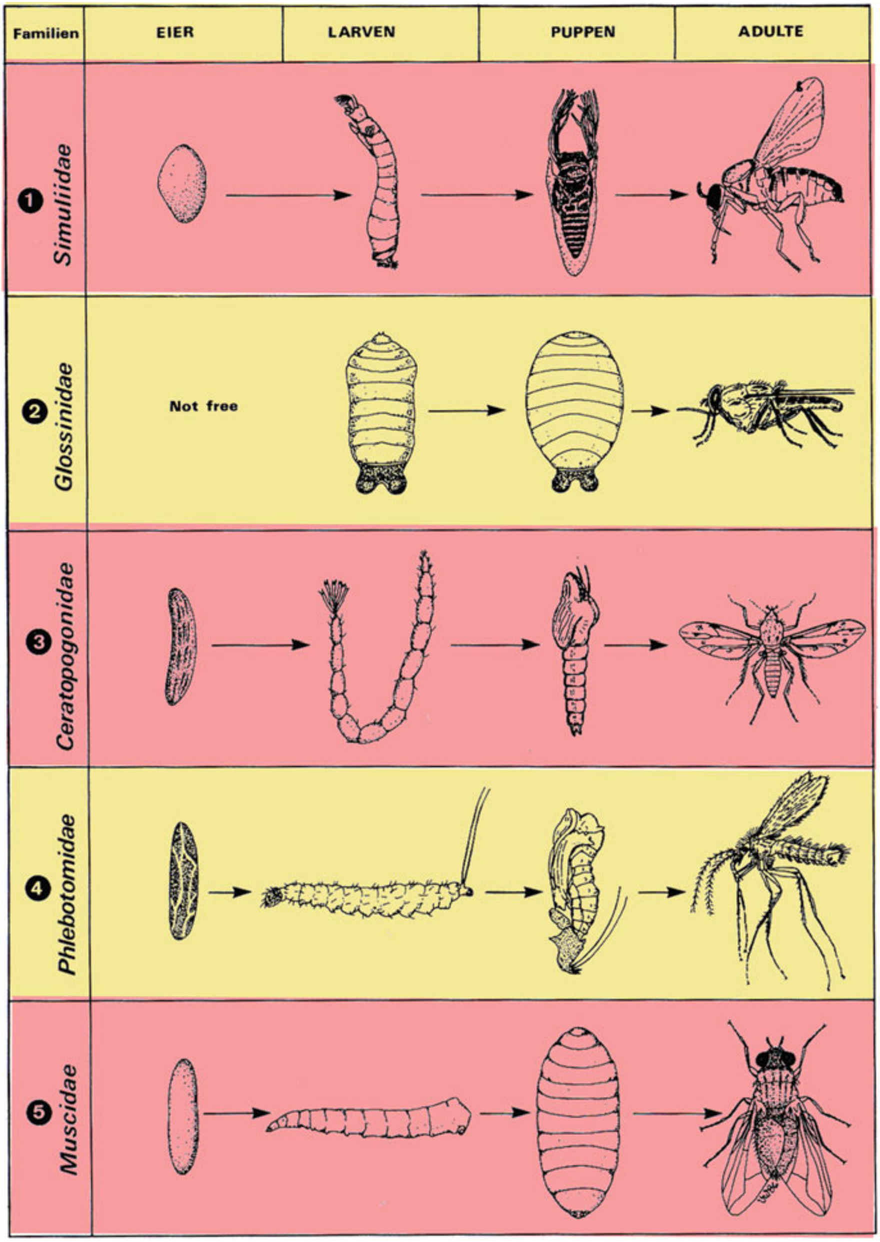
Precautions are needed because many species of insects either suck blood or settle on the skin or are contaminated with pathogens or are simply annoying.

5.6.1 Protection from Mosquitoes

1. Installation of mosquito screens before windows.
2. Empty the rain barrels regularly (once a week) including the sediment, since adult mosquitoes may hatch from the pupa stage within this time.
3. Insert frogs and fish in garden ponds and proceed treatment with *Bacillus thuringiensis*, if necessary.
4. Protection from sticking can be done by application of repellents onto skin and clothes (e.g. Viticks®, Autan®).
5. Treat the fur and skin of dogs with insecticides (the protection keeps up to 4–6 weeks).

◄

Fig. 5.93 (continued) Sucking apparatus in cross section. (**c**) **Piercing-sucking mouthparts of a mosquito**: (**1**) head of a female mosquito, sideview. (**2**) Biting apparatus in cross section. (**3**) Piercing a capillary in the skin. The labium will not be inserted. *AR* arista; *AT* antenna; *CL* clypeus; *HA* haustellum; *HY* hypopharynx with salivary duct; *LA* labrum; *LB* labium; *LL* labellum (with grooves for saliva distribution); *MD* mandibles; *MT* maxillary palp; *MX* maxilla; *N* food channel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❷ Glossinidae
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❸ Ceratopogonidae
❹ Phlebotomidae
❺ Muscidae

Fig. 5.94 Diagrammatic representation of the development of different groups of Diptera

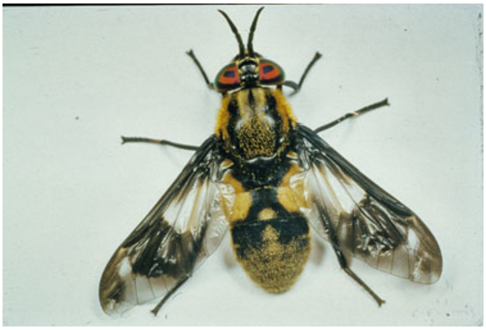

Fig. 5.95 Dorsal view of a *Chrysops* tabanid

5.6.2 Protection from Flies

1. Installation of mosquito screens before windows.
2. Do not leave food open at room temperature for long.
3. Do not put food onto the compost heap.
4. Never leave garbage bins open.
5. Remove feces of animals from the garden and other places close to the home.
6. Use a swatter whenever needed.
7. Install sticky flypapers in rooms—an old but very effective method.

5.7 Vampire Fish

The so-called **Candirus** (caneros) or vampire fish possess two hook-like teeth in their mouth. By the help of these teeth they can penetrate into the skin and gills a.s.o. of their hosts (fish, mammals) in order to suck blood.

Species: ***Vandellia cirrhosa.*** In many cases, they penetrated into the bladder, in the nose cavity, in mouth or into the skin of humans as stages of about 3 mm in length. This penetration always induced massive inflammation reactions in the afflicted organs if not a sepsis. The only way of therapy is to remove the parasite mechanically, if it is not expelled within the urine. However, they may die inside of the human body, too.

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5.8 Vampire Bats

Some species of bats living in South and Central America are able to induce lesions in the skin of mammals with their sharp teeth. They lick the extruding blood, while their "hosts" (cattle, horses, sheep, goats or humans) sleep outdoors at night.

This is well known for some species of the genus *Desmodus, Diaemus* and *Dipyhlla*, the so-called **Chupacapras**. While licking the blood, these vampire bats may transmit the pathogens of rabies, but also those of other animal diseases (Derringue bovine, Mal de Caderas). Most of the bat species, however, feed insects or fruits and thus attacks of humans remain scarce.

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Questions to Test Obtained Knowledge

Only one answer is correct!

1. **Which is the pathway of human infections by *Trichomonas vaginalis*?**
   (a) Diaplacentally
   (b) During close contact with cats
   (c) Taking up cysts orally
   (d) During sexual intercourse
   (e) Swallowing water while bathing
2. **How to become infected with the agent of Chagas disease *Trypanosoma cruzi*?**
   (a) Via infected meat
   (b) Directly by bite of an infected mosquito
   (c) Directly by bite of an infected bed bug
   (d) By infectious feces of a triatomine bug
   (e) By ingestion of cysts
3. **How to become infected with *Sarcocystis* species?**
   (a) By the bite of a mosquito
   (b) Diaplacentally
   (c) During sexual intercourse
   (d) Through close contact to dogs
   (e) By eating raw meat containing cysts
4. **The process of multiplication inside the tissue cysts of *Toxoplasma* and *Sarcocystis* are:**
   (a) A special type of sporogony
   (b) A special type of schizogony, during which numerous schizogonies take place within the cyst
   (c) A special form of schizogony, during which numerous endodyogonies take place within the cyst
   (d) A multiplication instead of sporogony immediately starting after the gamogony
   (e) Part of a gamogony

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5. **How to avoid infection of *Toxoplasma gondii*?**
   - (a) Connatally-diaplacentally
   - (b) By taking up meat containing cysts
   - (c) Through close contact with dogs
   - (d) During close contact with cats
   - (e) By oral uptake of sporocysts inside oocysts
6. **The so-called cercaria dermatitis is caused by:**
   - (a) Purulence of *Schistosoma* eggs
   - (b) *Trichomonas*
   - (c) *Ancylostoma*
   - (d) Penetration of unspecific cercariae of *Schistosoma* species into the skin
   - (e) Penetration of miracidiae into the skin
7. **Which sequence of stages is valid for S*chistosoma* species?**
   - (a) Adult-coracidium-redia-cercaria
   - (b) Adult-miracidium-sporocysts-cercaria
   - (c) Adult-miracidium-sporocysts-redia-cercaria-plerocercoid
   - (d) Adult-miracidium-sporocysts-redia-cercaria
   - (e) Adult-miracidium-sporocysts-cercaria-metacercaria
8. **Which of the following statements on *Schistosoma* species is correct?**
   - (a) The female of *Schistosoma* envelopes the smaller male with its widened side parts.
   - (b) The schistosomula must reach the human blood vessels.
   - (c) The eggs of the schistosomes must be ingested by snails.
   - (d) The redia of S*chistosoma* species produce cercariae in snails.
   - (e) The schistosomes combine to form pairs in the bladder of the host and lay eggs.
9. **A patient suffers from bilharziasis. How was he infected?**
   - (a) By taking up worm eggs orally with drinking water
   - (b) By taking up metacercariae orally
   - (c) By taking up cysticerci within raw (mostly minced) pork
   - (d) While bathing in a lake by the active penetration of cercariae into the skin
   - (e) While bathing by the active penetration of miracidia into the skin
10. **How does *Opisthorchis (=Clonorchis) sinensis* get into the human body?**
    - (a) By ingestion of raw (mostly minced) pork
    - (b) By bites of mosquitoes
    - (c) The cercariae penetrate actively into the human skin
    - (d) In the stage of the egg by contaminated drinking water
    - (e) By ingestion of raw meat of fresh water fish
11. **How do the eggs of *Schistosoma* species get into the bladder?**
    - (a) Via urethra.
    - (b) They penetrate the bladder wall by the help of their egg sting.
    - (c) Via intestine.
    - (d) The eggs are layed in the bladder.
    - (e) By the help of tissue inflammations, they penetrate through the bladder wall.

12. **Which combination is correct?**
    - (a) *Diphyllobothrium*-fish-human
    - (b) *Taenia saginata*-pig-human
    - (c) *Hymenolepis*-human-bug
    - (d) *Dicrocoelium*-*Cyclops*-human
    - (e) *Ascaris*-dog feces-human
13. **Which one of the following statements about tapeworms in humans is wrong?**
    - (a) *Echinococcus* produces cysts in well-vascularized organs.
    - (b) The fish tapeworm can induce pernicious anaemia.
    - (c) A single proglottid can contain more than 50,000 eggs.
    - (d) Fish tapeworms always must occur as pairs as they are viviparous.
    - (e) Proglottids of *Taenia saginata* can actively leave the human intestine.
14. **Which one of the following statements is wrong?**
    Echinococcus granulosus:
    - (a) Does not occur in Europe any more.
    - (b) Infects humans in the egg stage via so-called smear infections.
    - (c) Can develop to cyst larvae but not to mature worms in humans.
    - (d) Occurs as cyst larvae in numerous herbivores.
    - (e) Adult worms constrict motile proglottids at their terminal pole.
15. **Which one of the following statements about *Taenia saginata* is wrong?**
    - (a) *Taenia* worms have no intestine.
    - (b) Proglottids of *Taenia* can actively leave the human intestine.
    - (c) *Taenia* worms generally occur solitary in the intestine of their host.
    - (d) Larvae reach the muscles via blood stream.
    - (e) Tapeworms absorb a lot of vitamin B_{12} in its longitudinal growing zone and thus induces a lack of vitamin B_{12} in the host.
16. **Which one of the following statements about *Echinococcus* is wrong?**
    - (a) *Echinococcus*, the tapeworm of the dog, has only 3–5 proglottids.
    - (b) The infection of dogs occurs by ingestion of eggs, which must lay outside for at least 10 days, so that the larvae can develop.
    - (c) The worm nearly never occurs solitary.
    - (d) The cysts of this tapeworm can develop in well-vascularized organs of humans.
    - (e) Humans are infected with eggs from dog feces.
17. **Which one of the following statements about the biology of *Taenia saginata* is wrong?**
    - (a) Larvae penetrate the human intestine wall.
    - (b) Mature proglottids with their eggs can leave the intestine actively.
    - (c) The elder proglottids copulate with younger ones.
    - (d) *Taenia saginata* does not possess a crown of hooks at the scolex.
    - (e) Larvae of *Taenia saginata* are smaller than 10 mm.
18. **How do tapeworms take up their food?**
    - (a) With the proboscis
    - (b) With its mouth by the help of its surrounding sucker

   (c) Through the tegument
   (d) Via phagocytosis of peculiar cells
   (e) By its ventral mouth
19. **Which one of the following statements on trichines is correct?**
   (a) Worms are transmitted from carnivore to carnivore by taking up muscle trichines.
   (b) Worms are transmitted from herbivore to carnivore by ingesting muscle trichines.
   (c) Eggs are excreted within the feces of herbivores.
   (d) Eggs are excreted within the feces of carnivores.
   (e) The transmission occurs orally by female parasites hatching in the intestine.
20. **Which one of the following statements about roundworms is wrong?**
   (a) After eggs are laid in the mesenteria of the intestine or the bladder, they reach the lumen of the intestine or the bladder due to inflammatory processes.
   (b) Eggs need a time of stay in the open air.
   (c) Larvae can already slough their skin in the egg shell.
   (d) Larvae undergo a passage through the portal vein.
   (e) Muscle cells of the adults form protrusions to the nerves.
21. **Which one of the following statements is correct?**
   (a) *Ascaris* larvae penetrate the skin of human hosts.
   (b) Infection with *Enterobius (Oxyuris) vermicularis* can be induced either by taking up eggs orally or by invasion of larvae into the anus and colon.
   (c) All female filariae try to leave the human skin in order to lay their eggs into the water.
   (d) Humans are infected by *Ancylostoma* by ingestion of eggs.
   (e) Infections with nematodes happen only by eating contaminated food with eggs.
22. **The infection with hookworms occurs:**
   (a) Through penetration of cercariae into the skin while bathing
   (b) During the bite of blackflies
   (c) By ingestion of fertile eggs with the food
   (d) By ingestion of raw meat
   (e) By active penetration of filariform larvae
23. **Which of the following statements on *Trichinella spiralis* is correct?**
   (a) Fertile adult stages of *T. spiralis* can only be found in humans.
   (b) Young trichines reach the human blood via lymph vessels of the intestine.
   (c) *T. spiralis* lays its eggs into the intestine mucosa of humans.
   (d) Humans are infected with *T. spiralis* by the ingestion of raw beef.
   (e) Cattle is infected with *T. spiralis* by contaminated plant food.
24. **The infection of cattle with *T. spiralis* occurs:**
   (a) Not at all
   (b) By uptake of worm eggs within contaminated food
   (c) Via mosquito bites

   (d) By ingestion of metacercariae at the tip of grass blades
   (e) By viviparous larvae, which penetrate into the skin

25. **Acanthocephalans are:**
   (a) Worms without intestine
   (b) Ectoparasites of amphibians
   (c) A special group of trematodes, the so-called monogeneans
   (d) Cestodes, belonging to the group of Caryophyllidea
   (e) Blood-sucking nematodes
26. **Elephantiasis is induced by:**
   (a) *Wuchereria bancrofti*
   (b) *Loa loa*
   (c) *Dracunculus medinensis*
   (d) *Leishmania*
   (e) *Furunculosa vitiosa*
27. **The agents of the plague are transmitted by:**
   (a) Bites of ticks
   (b) Feces of lice
   (c) Bites of the rat flea
   (d) Bites of ants
   (e) Feces of sand fleas
28. **Which of the following statements is correct?**
   (a) Lice can only survive with symbionts, which therefore have to be transferred into the eggs by the female louse.
   (b) The trichobothria of the pygidial plate of fleas are used for the perception of attractants being excreted by the host.
   (c) In case of the mosquitoes, the first maxilla forms a saliva channel and the second maxilla is the tube for blood sucking.
   (d) The females of the mosquitoes have no wings.
   (e) Body lice transmit the agents of spotted fever exclusively while sucking blood.
29. **Which agents of disease are not transferred during blood sucking?**
   (a) The pathogens of the Chagas disease by bed bugs
   (b) Microfilariae by tabanids or mosquitoes
   (c) Agents of encephalitis by ticks
   (d) Rickettsiae by ticks
   (e) Agents of plaque by fleas
30. **Which of the following statements is correct?**
   (a) Body lice digest the sucked blood hidden behind loose wallpaper, picture frames and so on.
   (b) Bed bugs transmit the spotted fever.
   (c) Malaria-transmitting mosquito species do not occur in Germany.
   (d) Fleas are able to transmit the pathogens of yellow fever, of infectious dropsy, of encephalitis as well as filariae.
   (e) The bed bug normally does not transmit any pathogen.

31. **The pathogens of the human malaria are transmitted by:**
    (a) Female blackflies
    (b) About two species of the genus *Culex*
    (c) About 60 species of the genus *Anopheles*
    (d) Females belonging to the genus of *Aedes*
    (e) Males and females of the Tsetse fly
32. **Which combination of vectors and diseases is correct?**
    (a) Flea: plaque, scabies and spotted fever
    (b) Tick: Texas fever, tularaemia and trichomoniasis
    (c) Bed bug: typhus, plaque and trichomoniasis
    (d) Mosquitoes: filariasis, yellow fever and malaria
    (e) Crab louse (pubic louse): typhus, syphilis and maroditis
33. **The distribution of body lice increases. Which determining feature combination is significant for these parasites?**
    (a) A maximum of three pairs of legs and a Haller's organ
    (b) A maximum of three pairs of legs with claws (cling legs) and the absence of wings (apterism)
    (c) Piercing sucking mouthparts and halters
    (d) Pupae and no wings
    (e) Mycetomes with symbionts and parthenogenesis
34. **What is a myiasis?**
    (a) A virus infection transmitted by mosquitoes
    (b) A bacterial infection transmitted by biting houseflies (i.e. *Stomoxys*)
    (c) A rickettsiosis
    (d) Disease induced by wandering larvae of flies
    (e) Disease caused by wandering worm larvae
35. **Which determining features are significant for adult ticks?**
    (a) Three pairs of legs and the absence of wings (apterism)
    (b) Wings and piercing mouthparts
    (c) Piercing mouthparts and four pairs of legs
    (d) Four pairs of legs and two pairs of maxillae
    (e) Tracheoles and halters
36. **Which of the following combinations of vector and disease is correct?**
    (a) Bug-plaque-scabies
    (b) Mosquito-malaria-filariasis
    (c) Flea-trichinellosis-bilharziosis
    (d) Louse-rickettsiosis-yellow fever
    (e) None of the suggested possibilities
37. **How to transmit the pathogens of spotted typhus?**
    (a) By fleas when sucking blood
    (b) By feces of lice
    (c) By feces of bugs
    (d) Due to skin mining mites
    (e) By ticks when sucking blood

38. **Which one of the following statements is wrong?**
    (a) Male mosquitoes transmit malaria when blood sucking.
    (b) Females of the head louse attach their eggs to the head hair of humans.
    (c) Female and male ticks of *Ixodes ricinus* can transmit pathogens of encephalitis.
    (d) Male fleas suck blood, too.
    (e) Female body lice transfer symbiotic bacteria into their eggs.
39. **Scabies mites are actually progressing. Which of the following statements is correct?**
    (a) Scabies mites live on the skin.
    (b) They have piercing mouthparts and suck blood.
    (c) They dig tunnels in the epidermis.
    (d) They suck lymph fluids.
    (e) They feed on house dust.
40. **Which of the following statements is correct?**
    (a) The bed bug transmits the agents of spotted fever.
    (b) The bed bug does not transmit pathogens.
    (c) Blackflies transmit leishmaniasis.
    (d) Malaria-transferring mosquitoes do not occur in Germany.
    (e) *Leishmania* stages are transmitted by *Culex* mosquitoes.
41. **Which one of the following statements is correct? The flour mite transmits the agents of:**
    (a) Toxoplasmosis
    (b) Typhus
    (c) Scabies
    (d) Amoebic dysentery
    (e) No disease
42. **How is the infection pathway of malaria to humans?**
    (a) Females of the genus *Anopheles* transmit sporocysts.
    (b) Males of the genus *Anopheles* transmit sporozoites.
    (c) Females of the genus *Glossina* transmit merozoites.
    (d) Females of the genus *Anopheles* transmit gamonts.
    (e) Females of the genus *Anopheles* transmit slender sporozoites.
43. **Which one of these statements is wrong?**
    (a) Hydatids are the larvae of the pig tapeworm *Taenia solium*.
    (b) Sporocysts are multiplication stages of trematodes in snails.
    (c) The metacercariae of some trematodes can be observed in the muscle of fish.
    (d) The larva 3 of *Necator americanus* lives outside of the body.
    (e) *Echinococcus multilocularis* worms may occur in large numbers in the intestine of fox, dog and cat.
44. **Which combination of parasitic stage and afflicted organ is wrong?**
    (a) Liver: malaria schizonts and eggs of schistosomes
    (b) Liver: cysts of *Entamoeba* and larvae of *Ascaris*
    (c) Liver: *Clonorchis sinensis* and *Enterobius vermicularis*

(d) Eye: adults of *Loa loa* and larvae of *Onchocerca volvulus*
(e) Skin: *Sarcoptes scabiei* and larvae of *Onchocerca volvulus*

45. **Which is the pathway of infection for humans in case of the cattle tapeworm *Taenia saginata*?**
    (a) There is no way of infection.
    (b) Ingestion of cysticercus in raw beef.
    (c) By consumption of worm eggs.
    (d) Taking up cysticercus in small crustaceans.
    (e) By hydatids in raw beef.
46. **Which statement is wrong?**
    (a) Cestodes feed through their suckers.
    (b) The intestine of the trematodes is bifurcated and terminally closed.
    (c) Schistosomes live in the blood vessels of their hosts.
    (d) Nematodes can be transmitted by mosquitoes.
    (e) *Ancylostoma* larvae penetrate actively into the human skin.
47. **The so-called *Cysticercus cellulosae* is:**
    (a) The larva of the dog tapeworm *Echinococcus granulosus*. It can be situated in the muscles of sheep.
    (b) The larva of the dog tapeworm *Taenia pisiformis*. It can occur in the liver of sheep.
    (c) The larva of the tapeworm *Taenia solium*.
    (d) The larva of schistosomes.
    (e) The larva of the Chinese liver fluke, which is situated exclusively in the muscle of fish.
48. **The infection with roundworms of the genus *Ascaris* takes place by:**
    (a) Ingestion of freshly layed eggs with contaminated salad and so on
    (b) Ingestion of eggs having been stored outdoors for a long while
    (c) The ingestion of cysticercus in insufficiently cooked meat
    (d) Percutaneous penetration of rhabditiform larvae
    (e) Percutaneous penetration of filariform larvae
49. **Which combination is wrong?**
    (a) Rat flea-*Yersinia pestis*
    (b) Body louse-*Rickettsia prowazekii*
    (c) Bed bug-*Trypanosoma cruzi*
    (d) Tsetse fly-*Trypanosoma brucei rhodesiense*
    (e) Sandfly-*Leishmania donovani*
50. **Which statement is correct?**
    (a) The cercariae of *Clonorchis sinensis* penetrate into the human skin.
    (b) The cercariae of *Schistosoma japonicum* at first penetrate into the fish and are transformed to metacercariae there.
    (c) The cercariae of *Echinococcus granulosus* penetrate into the liver via blood vessels.
    (d) The cercariae of *Schistosoma* penetrate into the skin of humans and move as schistosomula to the portal veins.
    (e) The infection with *Schistosoma* stages occurs by ingestion of metacercariae in raw muscles of fish.

51. **How can an infection with *Schistosoma haematobium* be diagnosed?**
    (a) By the proof of eggs with a lateral spike in the human feces
    (b) By the proof of eggs with a terminal spike in human urine
    (c) By the proof of eggs with a terminal spike in human sputum
    (d) By the proof of eggs with a terminal spike in the feces
    (e) By the proof of eggs with a lateral spike in the urine
52. **The infection with *Ascaris lumbricoides* takes place by:**
    (a) Ingestion of pork meat containing larvae
    (b) Active penetration of free larvae into the skin
    (c) Ingesting eggs containing an infectious larva
    (d) Ingestion of free larvae with contaminated salad
    (e) Uptake of drinking water containing small crustaceans with larvae
53. **Which combination of organ and position of the adult worms is wrong?**
    (a) *Dracunculus medinensis* – subcutaneous tissue
    (b) *Schistosoma mansoni* – blood vessels of the mesenteria of the intestine
    (c) *Clonorchis sinensis* – small intestine
    (d) *Ancylostoma duodenale* – small intestine
    (e) *Trichinella spiralis* – small intestine
54. **Which statement is wrong?**
    (a) Bed bugs do not transmit pathogens.
    (b) Triatomid bugs transmit trypanosomes.
    (c) *Sarcoptes scabiei* mites do not transmit pathogens.
    (d) The so-called baker's scabies is an allergic reaction on contact with cockroaches of the genus *Blatta*.
    (e) Ticks transmit the pathogens of piroplasmosis of farm animals.
55. **Which statement is correct?**
    (a) Flies never suck blood while all mosquitoes do it.
    (b) Only female fleas suck blood, but they transmit the pathogen of the plague via feces.
    (c) Males and females of the body lice suck blood. The infection of humans with the pathogen of the spotted typhus takes place by breathing in of lice feces though.
    (d) Both genders of *Anopheles* mosquitoes transfer the pathogen of malaria.
    (e) Males and females of the body lice transmit spirilles when sucking.
56. **Which combination is correct?**
    (a) Ascariasis-phlebotomids – Ile de France
    (b) Maroditis perniciosa-louse – South East Bavaria
    (c) Cysticercosis-mosquitoes – Venezuela
    (d) Leishmaniasis-sandfly – Baleares
    (e) Filariasis-tick – Germany
57. **What is the main symptom of the Lyme borreliosis?**
    (a) Rosacea migrans
    (b) Perpendula periodica
    (c) Erythema irritans
    (d) *Tunga penetrans*
    (e) Urticaria molestans

58. **Which arthropods are the vectors of the agent of the Lyme borreliosis?**
    (a) All argasid ticks
    (b) All pigeon ticks
    (c) The *Ixodes* ticks
    (d) The bed bug
    (e) The brown dog tick
59. **The agents of the TBE (tick-borne encephalitis) are:**
    (a) *Rickettsia* stages, which are transmitted via feces of lice
    (b) Viruses transmitted by *Ixodes ricinus*
    (c) M*ycoplasma* stages transmitted by fleas
    (d) Protozoans transmitted by the tick *Ixodes ricinus*
    (e) *Anaplasma* stages transmitted by the tick *Ixodes ricinus*
60. **Cerebral malaria occurs:**
    (a) As a result of blocking of the blood flow in the capillaries of the brain due to adhesion of *Plasmodium* stages containing erythrocytes
    (b) Due to blocking of the capillaries by special stages of *Toxoplasma gondii*
    (c) Due to blocking of the capillaries by *Cysticercus neuronalis*
    (d) Caused by lysis of erythrocytes, which were infected by *Plasmodium* gamonts
    (e) By fusion of macrophages with helper T-cells in the brain infected with *Trypanosoma brucei rhodesiense* or *T.b. gambiense*

Solutions

1d; 2d; 3e; 4c; 5c; 6d: 7b; 8b; 9d;10e; 11e; 12a; 13d; 14a; 15e; 16b; 17a; 18c; 19a; 20a; 21b; 22e; 23b; 24a; 25a;26a; 27c; 28a; 29a; 30e; 31c; 32d; 33b;34d; 35c; 36b; 37b; 38a; 39c; 40b; 41e; 42e; 43a; 44c; 45b; 46a; 47c; 48 b; 49c; 50d; 51b; 52c; 53c; 54d; 55c; 56d; 57a; 58c; 59b; 60a.

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